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Recurrent implantation failure: a plea for a widely adopted rational definition

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ABSTRACT

Most proposed definitions of recurrent implantation failure (RIF) are based on clinical judgement, probably affected by patients' demands. They are not based on robust statistical considerations. As a result, a diagnosis of RIF is commonly made too early, exposing couples to the risk of overdiagnosis and overtreatment. However, the situation is changing, and three statistical approaches have recently been proposed. The first is a probability model based on the chances of success per cycle and suggests for the definition three failed oocyte retrieval cycles with all embryos being transferred in women younger than 40 years of age. The second approach suggests an individualized diagnosis that takes into consideration multiple factors, while the third is also based on individualization but mainly relies on anticipated euploidy rates across the female age range. All these approaches have their pros and cons. Regardless of the specific peculiarities, they represent steps in the right direction, with the intent of providing a statistically sound definition. However, these attempts will not be useful unless endorsed by the scientific community in general. There is a pressing need for a rigorous and shared definition of RIF that will be widely accepted by researchers, scientific societies and other stakeholders, including patients.

INTRODUCTION

The risk of failure is typically higher than the chance of success in an assisted reproductive technology cycle at any age. As a resultant, a substantial proportion of couples fail to achieve a pregnancy after two to three cycles, but most will succeed if they persist on treatment. The cumulative chances of live birth after six cycles have been estimated to exceed 80% in couples with a good prognosis (*Smith et al., 2015*). Perseverance is essential for success in the battle with infertility.

The management of repetitive failures is challenging for both couples and healthcare providers. Pure statistical considerations provide little relief in clinical practice, and an approach of heralding success in the long term is unsatisfactory for most patients. Drop outs are common, approaching 30–50% even in good-prognosis couples (*Busnelli et al., 2020*). In addition, after one or more failed cycles, patients typically ask for additional investigations to meet their unsatiable need to identify an underlying cause. Physicians frequently give in to this request, exposing couples to undue risks and costs (*Ata et al., 2021*; *Somigliana et al., 2018*).

DEFINITION OF RECURRENT IMPLANTATION FAILURE

Recurrent implantation failure (RIF) presumably exists. The presence of functional endometrial disruptions impeding embryo implantation is biologically plausible. Moreover, RIF is not necessarily limited to an endometrial aetiology as couples can also repeatedly

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generate embryos that are unable to implant; generating aneuploid embryos more often may, for example, be one of several such reasons.

Unfortunately, a widely agreed-upon definition of RIF is not available. A plethora of definitions have been used so far (*Polanski et al., 2014*) and most are based on clinical rather than scientific judgement. They vary in the selection criteria (generally aimed at excluding poor-prognosis couples), number of cycles, number of embryos transferred, quality and developmental stage of the embryos transferred, use of preimplantation genetic testing for aneuploidies (PGT-A) and definition of failure (including or excluding biochemical pregnancies) (*Polanski et al., 2014*). The most cited definitions generally refer to two to three failed cycles in good-prognosis women.

Not only recurrent failures, but even one failure warrants re-ascertainment and discussion with the couple, regardless of a frank diagnosis of 'RIF'. This is an undisputable need for patients. Patients' expectations and statistical calculations do not, however, overlap. This clinical need should not determine the definition of RIF. A definition based on patients' needs or clinical judgement may result in a premature, unsubstantiated diagnosis of 'RIF', exposing couples to risks of overdiagnosis and overtreatment (*Somigliana et al., 2018*).

Recently, shortcomings of the available definitions have been recognized by different groups and new definitions based on more robust scientific considerations have been proposed (*Ata et al., 2021*; *Rozen et al., 2021*; *Somigliana et al., 2018*). These novel approaches will be briefly reviewed here.

PURE PROBABILITY CALCULATIONS

The first approach was based on a simple mathematical model (*Somigliana et al., 2018*). RIF was considered as a dichotomous condition; i.e. couples are either affected or unaffected by a condition that absolutely prevents implantation. The chance of success for unaffected individuals was assumed to be constant while that for those who were affected was assumed to be nil. In this model, the chances of success progressively declined with an increasing number of attempts because the relative proportion of individuals with RIF increased in the denominator.

Unfortunately, this model remains theoretical because the true rate of RIF, which has a significant impact on the model, is unknown. Therefore, a clinical study was undertaken that aimed to disentangle the two variables of the model, i.e. the rate of RIF and the rate of IVF success per cycle in couples without RIF (*Busnelli et al., 2020*). Overall, 1221 women younger than 40 years and without abnormalities of the uterine cavity or hydrosalpinx were selected. Women were excluded if no embryos could be obtained for transfer at any cycle. Applying the theoretical model to the data, a 15% rate of RIF and a 61% rate of cumulative success per cycle in women without RIF were extrapolated. On this basis, RIF was defined by three failed attempts including three oocyte retrievals and all subsequent transfers. According to this definition, the false-positive rate (i.e. the probability of labelling it 'RIF' when it was only misfortune) was deemed acceptable, being 1 in 4 cases (25%) (*Busnelli et al., 2020*).

The most important limitation of this model is that it disregards the couples' baseline prognostic factors.

INDIVIDUALIZED DIAGNOSIS: THE NEW ERA

There is an evident link between poor prognostic factors and RIF. Women's age and ovarian reserve are too important as determinants of IVF success to be disregarded (*Polyzos et al., 2018*; *Smith et al., 2015*). Two distinct groups tried to address this problem and proposed individualized definitions of RIF (*Ata et al., 2021*; *Rozen et al., 2021*).

Rozen and colleagues (*Rozen et al., 2021*) introduced the concept of 'theoretical cumulative implantation rate' (TCIR). This can be calculated by summing the anticipated implantation rate for each previous embryo transfer. An estimation of implantation rate for each transfer would consider multiple factors including but not limited to female age, quality, stage and number of previously transferred embryos and types of cycle, preferably with the centre's own data or registry data. For instance, a 28-year-old woman with three top-quality embryos transferred (assumed a probability of implantation of 0.4 for each embryo) has a failure probability of 0.22 (i.e. 0.6^3). Her TCIR would therefore be 0.78 (1 – 0.22). The authors did not define in detail how to calculate the anticipated implantation probability per embryo or provide a clear indication of the threshold of TCIR that should be called RIF, suggesting either an arbitrary 80% (based on a presumed RIF frequency of 10–15%) or adapting to the local success rates. Referring to the first option, the abovementioned woman would not be diagnosed with RIF as her TCIR of 0.78 is less than 0.80. However, if she failed to become pregnant with another embryo, she would fulfil the criterion ($1 - 0.6^4 = 0.87$) (*Rozen et al., 2021*).

The main limitations of this include the dichotomous vision of RIF (as in the previous model) and the assumption of the independence of embryos. Considering embryos obtained from the same oocyte retrieval as being independent in their capacity to implant may not be correct from a strict statistical standpoint (*Roberts and Stylianou, 2012*). Moreover, it is unclear which prognostic factors would be included in the calculation of implantation potential of each embryo to inform the TCIR and how those data could be collected in real life.

Subsequently, an individualized diagnosis of RIF with more elaborate statistics has been proposed (*Ata et al., 2021*). The model was conceived only for women receiving blastocysts and is based on the consideration that embryo aneuploidy stands out as the most common cause of failure. Therefore, RIF can be diagnosed only after the transfer of an adequate number of euploid embryos without success when the cumulative expected chance of implantation would exceed 95%. This threshold was suggested by a similitude with the conventional type I error rate of 0.05, a cut-off commonly used to infer statistical significance. The authors speculate that a less stringent limit of 0.9 could be sufficient. Considering that euploid blastocysts have a chance to implant of between 45% and 65% regardless of age, the unsuccessful transfer of 3–5 euploid blastocysts is required to diagnose RIF (as then the expected cumulative probability exceeds 95%). Interestingly, this theoretical assumption fits with a recent observation showing a cumulative pregnancy rate of 95% with the transfer of three euploid

embryos in women with unremarkable uterine conditions (*Pirtea et al., 2021*).

The model is simple for couples performing PGT-A but becomes slightly more complicated for those who are not. In this latter situation, the number of embryos to be transferred for the diagnosis should be calculated based on the woman's age because of the well-known relationship between age and aneuploidy. For instance, for the abovementioned 28-year-old woman, this would correspond to the transfer of 6–9 blastocysts, depending on the anticipated implantation rate of euploid blastocysts, for a diagnosis of RIF. A simple Excel file to allow readers to adapt the model to their own figures was provided with the manuscript (*Ata et al., 2021*).

COMMENTS

RIF has ignited a burning debate over the last decade. While some authors have denied its mere existence (*Evers, 2016*), the literature on treatments for the condition has expanded rapidly (*Busnelli et al., 2021*). Certainly, the management of repetitive failures represents a clinical need. Women who experience several failed transfers are devastated and physicians must handle this emotional difficulty. Drop outs, overdiagnoses and overtreatments are important concerns in this situation.

Clearly delineating RIF is particularly important from a research perspective. Studying well-defined cases will allow the discovery of possible novel mechanisms of implantation failure. As a result, new treatments may be developed and studied. Even more promising, once a new cause and its treatment are discovered, it will not be necessary to wait until several failures have occurred before treating the condition. These can be rapidly incorporated into the basal assessment of infertility to avoid a fruitless exposure to several unsuccessful cycles.

A widely accepted valid definition of RIF is also important from a clinical perspective. Even if a definitive diagnosis may be burdensome because of the questionable efficacy of currently proposed therapeutic options (*Busnelli et al., 2021*), it can still empower couples. Moreover, it can benefit couples with conditions such as intramural fibroids, adenomyosis or uterine septa, which impact embryo implantation but there is no proven treatments (*Ata et al., 2021*). The couples may have embarked on IVF without treatment for these conditions, but once they have been diagnosed with RIF, physicians and patients may reconsider their decision and decide to intervene.

The three papers discussed above represent an important step forward. They introduce a novel view. The criteria for diagnosis should be guided by statistical considerations and not by patients' demands or clinical judgement. The individualized approaches proposed by Rozen and colleagues and Ata and co-workers are more complex but also more attractive because they consider two essential prognostic factors of IVF: the woman's age and the number of embryos (*Ata et al., 2021*; *Rozen et al., 2021*).

However, some uncertainties remain. For widespread acceptance of an individualized definition, there is first the need to precisely decide on the threshold of probability for the diagnosis (expected success of 80%, 90% or 95%?). Neither group was trenchant on this point (*Ata et al., 2021*; *Rozen et al., 2021*). Second, would it be more appropriate to refer to standardized expected rates of success or to rely on local or the group's own figures? The former option would simplify the application of a model; the latter would better endorse the complexity of the topic. Third, the assumption of an independence of embryos simplifies the calculations but may introduce some imprecision. How relevant this simplification is for the validity of a model needs to be investigated. To note, even if this model is not individualized, only the first illustrated model overcomes the issue of independency as the definition was based on failed cycles and not on number of embryos transferred. Finally, any individualized model would need to be validated.

CONCLUSIONS

These recent efforts to provide a reproducible diagnosis of RIF will not be useful if they are not endorsed by the scientific community. We are at a critical juncture with some valuable options on the table. A reproducible definition of RIF that will be widely accepted by researchers, scientific societies and other stakeholders, including patients, is needed. Such a definition could mark a starting point for real progression.

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