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Short title: Definition of repeated implantation failure

Repeated implantation failure at the crossroad between statistics, clinics and over-diagnosis

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Key message

The commonly used definition of repeated implantation failure based on three failed IVF attempts leads to an exceedingly high number of false–positive diagnoses.

Author biography

Edgardo Somigliana graduated in Medicine in 1994, completed his residency in Obstetrics and Gynaecology in 1999 and obtained a PhD in Prenatal Medicine in 2006. He is the Head of the Infertility Unit of the Ospedale Maggiore Policlinico and Associate Professor in Obstetrics and Gynaecology.

Abstract

The most common definition of repeated implantation failure (RIF) is the failure to obtain a clinical pregnancy after three completed IVF cycles. This definition, however, may lead to misuse of the diagnosis. To disentangle this, we set up a mathematical model based on the following main assumptions: rate of success of IVF constant and set at 30%; and RIF postulated to be a dichotomous condition (yes or no) with a prevalence of 10%. On this basis, the expected cumulative chance of pregnancy after three and six cycles was 59% and 79%, respectively. Consequently, the false–positive rate of a diagnosis of RIF is 75% and 51%, respectively. Increasing the rate of success of IVF or the prevalence of RIF lowers but does not make unremarkable the rate of false–positive diagnoses. Overall, this model shows that the commonly used definition of RIF based on three failed attempts in a standard population with good prognosis leads to over-diagnosis and, potentially, to over-treatments.

KEYWORDS: repeated implantation failure, IVF, model, false positive

<A>Introduction

Repeated implantation failure (RIF) is mainly defined as the failure to obtain a clinical pregnancy after three consecutive IVF attempts, in which one to two embryos of high-grade quality are transferred in each cycle (Simon and Laufer, 2012). The precise definition, however, remains controversial, and several other different suggestions have been made. Considering the number of failed cycles, three completed IVF attempts is the most commonly used threshold (Polanski *et al*., 2014); however, in a minority but not negligible proportion of studies, a diagnosis is made after only two cycles (Polanski *et al*., 2014). It has been suggested that the focus should be on the number of embryos, and a definition of RIF has been proposed as the ineffective transfer of a total of 10 cleavage stage embryos or four blastocysts (Polanski *et al*., 2014). The definition of 'good-quality embryos' that is commonly used in these proposals is also a matter of concern (Coughlan *et al*., 2014a). In general, all the suggested definitions derive from expert opinions but lack robust scientific basis.

From a clinical viewpoint, RIF represents a challenging and frustrating condition. Physicians have to handle stressed couples who are frequently overwhelmed by the situation (Coughlan *et al*., 2014b). Failure to achieve pregnancy is one of the main reasons explaining the high rate (up to 50%) of couples who drop-out from IVF programmes after fewer than three cycles (Gameiro *et al*., 2012; Gameiro *et al*., 2013). Those who do not give up desperately ask for more in-depth diagnostic investigations or adjuvant treatments aimed at improving their chances of pregnancy. Even if the pregnancy rate was not shown to markedly reduce with the number of attempts (Luke *et al*., 2012; McLernon *et al*., 2016), physicians frequently irrationally comply with these requests. This common clinical attitude is humanly understandable and may ultimately be helpful in improving long-term adherence to the IVF programme. On the other hand, it may waste financial resources and expose patients to undue additional risks.

In fact, given the relatively low rate of IVF success, three failed attempts has to be expected in a large proportion of couples even in the absence of any real obstacle to the success of the procedure. Even if RIF presumably does exist, currently used definitions may be insufficiently stringent. This can hamper research in the field and may lead to over-diagnosis and, potentially, to over-treatments. In this study, we aim to show that RIF represents a misused diagnosis using a mathematical model.

<A>Materials and methods

The primary aim of the mathematical model that we have elaborated was to evaluate the effect of the number of IVF cycles on the capacity to discriminate between couples who are actually affected by RIF (women who will never achieve pregnancy even after an infinite number of IVF attempts) from women who do not conceive just because of statistical misfortune.

The assumptions made for the model were as follows: rate of success of IVF (cumulative chance of pregnancy per oocyte retrieval) is constant; rate of success of IVF in women without RIF problems is 30% (EIM, 2016); RIF postulated to be a constant and dichotomous (yes or no) condition; and prevalence of RIF is 10%.

In fact, the real prevalence of RIF is unknown and arbitrarily set at 10% (but then varied in sensitivity analyses from 5 to 25%). Even if a precise estimation of this prevalence cannot be extrapolated from published research, data from two studies reporting on the cumulative chance of pregnancy after seven to eight treatments cycles suggest that the frequency of this condition is at least below 20% (Luke *et al*., 2012; McLernon *et al*., 2016). Indeed, in both studies, the cumulative chances excluding drop-outs (optimal estimate) exceeded 80%.

In our model, the analyses included up to six treatment cycles. Only women without RIF (corresponding to 90% of the cohort entering the IVF programme as 10% were affected by RIF)

could become pregnant. The IVF success rate (30% in the basal model) thus applied only to women who had not experienced RIF remaining in the cohort (those achieving pregnancy in one specific cycle were obviously excluded from the remaining cohort). For instance, in the basal model, the chances of pregnancy at first cycle was 27% (30% of the 90% of women not affected by RIF).

The false–positive rate of a diagnosis of RIF (FP) was calculated using the rate of RIF (A) and the rate of women without RIF who have not yet conceived because of statistical misfortune (B). Specifically, the formula was as follows:

$$FP = B / (A + B)$$

Sensitivity analyses was carried out on the rate of success of IVF (10–50%) and on the prevalence of RIF (5–25%).

<A>Results

The main results of the application of our model are presented in **Figure 1**. Women with RIF will never become pregnant regardless of the number of IVF attempts: therefore, even if they represent 10% of the initial cohort of women entering the programme, the relative proportion progressively increases with the number of attempts (women achieving pregnancy drop out). As a consequence, even if women not affected by RIF have a constant chance of becoming pregnant of 30% per cycle, the chances of pregnancy progressively decreases with the number of attempts. Specifically, the pregnancy rates are 27%, 26%, 25%, 23%, 20% and 18% at the first, second, third, fourth, fifth and sixth cycles, respectively (**Figure 1**, upper panel). The consequent cumulative chances of pregnancy grows progressively more slowly with the number of cycles, being 27%, 46%, 59%, 68%, 75% and 79% after first to sixth cycles, respectively (**Figure 1**, lower panel). Consequently, the false–positive rate of a diagnosis of RIF is 86%, 81%, 75%, 68%, 60% and 51%, respectively. In other

words, couples can be erroneously labelled with a diagnosis of RIF in four out of five cases after two cycles, three out of four cases after three cycles and in one out of two cases after six cycles.

Results from the two planned sensitivity analyses are presented in **Figure 2**. Increasing the rate of success of IVF from 10% to 50% lowers the rate of false–positive diagnosis of RIF. Specifically, the rate decreases from 88% to 69% after two cycles, from 87% to 53% after three cycles and from 83% to 12% after six cycles (**Figure 2**, upper panel). Modifying the rate of RIF in the population from 5 to 25% also affects the accuracy of the diagnosis of RIF. Specifically, the rate of false–positive diagnoses decreases from 90% to 60% after two cycles, from 87% to 51% after three cycles and from 69% to 26% after six cycles (**Figure 2**, lower panel).

<A>Discussion

A reliable diagnosis of RIF cannot be drawn after only two to three IVF cycles. Accuracy remains low even when strictly considering the definition proposed by Simon and Laufer (2012) of at least three complete IVF cycles transferring one or two high-quality embryos. Indeed, the rate of false–positive diagnoses after three IVF cycles remains above 50% in all sensitivity analyses. The diagnosis actually becomes more reliable after six cycles.

The model seems to be sensitive to the rate of success of the procedure. The diagnosis of RIF may be more reliable in patients who face chances of success up to 50%, for example, young women with appropriate ovarian reserve and those undergoing oocyte donation (Van Voorhis, 2007). Conversely, the diagnosis cannot actually be made in women with poor prognosis whose chances of pregnancy are below 10%, i.e. women aged over 40 years (Van Voorhis, 2007). In clinical practice, however, precisely discerning between good- and poor-prognosis couples is not always simple. The chances of pregnancy depend on patients' characteristics, such as age, ovarian reserve and cause of infertility, and IVF local policy, such as preimplantation genetic screening, extended culture, and

number of transferred embryos; however, a precise personalized estimate remains difficult (van Loendersloot *et al*., 2014; McLernon *et al*., 2016b; Sarais *et al*., 2016). Most importantly, the definition of good-prognosis women, and thus the reliability of RIF diagnosis, should also be adapted to the local context given the elevated inter-centre variability of the effectiveness of IVF (Lintsen *et al*., 2010). Finally, it is worthwhile noting that the diagnosis of RIF is facilitated if the condition has a high prevalence. Again, accuracy remains modest up to a prevalence of 25%, a presumably unrealistic rate considering that the cumulative chances of pregnancy after seven to eight cycles of IVF have been shown to be over 80% (Luke *et al*., 2012; McLernon *et al*., 2016a).

The clinical relevance of a false–positive diagnosis depends on the clinical context. If the causes can be reliably identified with cheap and safe investigations, and an effective and safe treatment is available, the importance decreases. Conversely, a high rate of false–positive diagnoses is unacceptable if the identification of the causes requires expensive, debated and risky investigations or if there is no definite evidence of effective treatments. Unfortunately, the IVF scenario is more evocative of the latter rather than of the former situation.

Discussing all the possible causes of RIF, the related diagnostic instruments and the possible therapeutic solutions is beyond the scope of our study. These arguments have been exhaustively reviewed recently (Simon and Laufer, 2012; Coughlan *et al*., 2014a; de Ziegler *et al*., 2016; Zohni *et al*., 2016). A tentative list of possible factors interfering with embryo implantation and possible treatments is shown in **Table 1** (Johnson *et al*., 2010; Practice Committee of ASRM, 2012; Brady *et al*., 2013; Li *et al*., 2013; Vercellini *et al*., 2014; Bosteels *et al*., 2015; Crawford and Steiner, 2015; Practice Committee of ASRM, 2015; Ata and Urman, 2016; de Ziegler *et al*., 2016; Ko *et al*., 2016; Practice Committee of ASRM, 2016; Robertson *et al*., 2016; Zuini *et al*., 2017). Of relevance here is that factors that are well-known to interfere with embryo implantation, and that are amenable to effective, economic and safe therapies, deserve to be identified and treated before embarking on an IVF programme. In fact, there is a general consensus that conditions such as smoking, obesity,

hydrosalpinx, uterine septum, endometrial polyps and submucosal fibroids type 0 and 1 should be corrected before starting IVF rather than after two or three failed attempts (Johnson *et al*., 2010; Practice Committee of ASRM, 2012; Brady *et al*., 2013; Practice Committee of ASRM, 2015; Practice Committee of ASRM, 2016). Once these factors are excluded (**Table 1**), one has to recognize that the remaining points are all controversial. Their role in the pathogenesis of RIF is debated or there is no demonstrated effective treatment. Oocyte donation represents an exception, but the validity of this option has to be balanced with the values and preferences of the patients.

Even if smoking, obesity, hydrosalpinx, uterine septum, endometrial polyps and submucosal fibroids are detrimental conditions that should be corrected before starting treatment cycles, some couples may be initially non-compliant, and may choose to directly enter the IVF programme. In these cases, physicians may consider re-discussing the opportunity of these interventions in couples who have experienced repeated failures. This upsetting clinical situation might improve adherence, particularly in challenging situations, such as when patients are required to stop smoking or lose weight.

Comment [S2]: Author: would 'value' be a more appropriate word than opportunity?

Some limitations of our model should be acknowledged. First, as for all models, the figures emerging from our analysis should be viewed as a mere estimation of the reality. Albeit practically complex, confirmation from real-word data is warranted. On the other hand, the robustness of the sensitivity analyses tends to support the reliability of the model. In fact, even in good-prognosis couples, setting the threshold at three failed cycles still exposes women to a significant risk of undue diagnoses of RIF (>50%). Similarly, the higher the rate of RIF, the lower the rate of false–positive diagnosis but, again, even in the extreme scenario of a prevalence of RIF of 25%, the rate of false–positive diagnoses after three cycles remains above 50%.

Second, a possible point of concern is the choice to consider RIF as a dichotomous and permanent condition, i.e. as a present or absent situation. From a biological perspective, it would be more plausible to consider RIF as a continuous condition varying from a weak effect (implantation can

occur but with a slightly lower chance) up to a definite detrimental effect (implantation will never occur, as it is stated in our model). Noteworthy, a reduced rate of implantation secondary to poor endometrial preparation or excess oestrogen effect or some other temporal factor that is not constitutive may indeed be remediable. Introducing a gradient effect in our analysis would lead to a significant complication of the model. In this context, it has to be pointed out that the scenario on the accuracy of the diagnosis could be worse if RIF is considered a continuous condition. The number of IVF cycles needed to draw a reliable diagnosis would need to be increased. On the other hand, one may appeal for a more clinical and pragmatic vision of RIF. The crux of the matter is the interpretation of the condition. If one restricts RIF to those who have a permanent block to embryo implantation, then the prevalence is likely to be low, and the number of cycles needed to reach the diagnosis is inevitably high. If one widens the definition based on everyday clinical practice (couples are generally upset after two or three failed cycles and strongly request for additional investigations and treatments), this may be more patient-centered but may expose couples to undue risks and useless additional expenditure. The theoretical model presented in our study cannot provide a definite solution. Our main aim was to warn the scientific community and stakeholders on the potential risks of a simplistic definition of RIF.

The observations emerging from our model have some relevant implications. First, they strengthen the need for an appropriate selection of the characteristics of the participants to be included in future studies of RIF. The use of six failed cycles in a population of very good prognosis may be idealistic but, on the other hand, selection criteria are essential if the scientific community aims at adequately investigating the pathogenesis and possible treatment of RIF. The inclusion of an exceedingly high proportion of normal patients may significantly dilute the results of observational and interventional studies. Even if more stringent criteria may markedly shrink the number of participants, researchers should aim at multicentre collaborations rather than incongruously widening these criteria. On the basis of our data, and accepting the inclusion of half non-affected patients, the possible definition of

RIF could be three failed IVF cycles in very good prognosis patients (50% expected rate of success) or six failed cycles in a normal IVF population (30% expected rate of success).

Second, our results may have some practical clinical implications. Physicians and patients have to adequately cope with the somehow cruel rules of statistics. Patients should be informed in-depth of the relatively low rate of success of IVF and the importance of persevering if they want to succeed. Moreover, physicians have to simplify the procedure of IVF as much as possible to reduce the general burden, make the procedure more friendly and ultimately improve adherence. Much attention should be paid to costs, regimen of stimulation, cycle monitoring and safety. Handling the psychological fragility of the couple facing this challenging situation is another independent important aspect. In fact, most couples experiencing repeated failures do not accept a comment 'that this happens'. Most will ask, if not demand, what possible scientific basis there might be for understanding and treating the failure they have experienced. The recently increased experience of patients who are told that 'perfect genetically normal' embryos are being transferred who fail to achieve pregnancy may have even worsened the situation. These patients will especially demand a further exploration of the reasons for failure, now that the time honored genetic reason for failure has been, supposedly, eliminated. In general, by not responding to this request for explanations, a clinician will risk losing his or her patient and thus impair the ultimate chance to achieve the goal. Physicians cannot deny a patient's experience and are called here to a challenging task, i.e. finding out the subtle equilibrium between rationality and psychology. The web-mediated exposure to the mermaid melodies on new 'magic' solutions do not facilitate this task.

In this context, we plea for a less stringent interpretation of RIF. Regardless of the precise number of cycles needed for the definition, RIF should not be viewed as a diagnosis but, instead, as a condition at increased risk of having a diagnosis that may interfere with implantation. Women with repeated failures should not be labelled with the diagnosis of RIF, but, conversely, as women with a condition meriting re-evaluation. In other words, RIF actually identifies a population that may

require more attention and, if needed, further testing to rule out a possibly treatable diagnosis. In general, the nature of screening requires high sensitivity and low specificity. On this basis, one could accept the currently used definitions of RIF. On the other hand, a diagnostic test requires high specificity to be a 'gold standard' and enter clinical practice. Prescribing tests of debatable accuracy, unlinked to effective therapies, or both, is questionable. Physicians should clearly keep in mind these aspects when managing couples with repeated failures and patients should be informed in-depth about the clinical and statistical logics that are behind their condition. Targeting patients with a diagnosis of RIF without explaining to them the overall logic behind this situation may be frustrating and even stigmatizing.

In conclusion, the current definition of RIF contrasts with the basic rules of statistics. Researchers have to deal with the intrinsic uncertainty of this diagnosis to design better studies aimed at investigating the causes and treatments of RIF. Moreover, physicians should also have a clear and realistic view of RIF to improve their ability to handle this clinically demanding situation. Of possible relevance here is clearly explaining *a priori* to the couples the intrinsic statistical rules of IVF (a procedure with a relatively low chance of pregnancy requiring multiple attempts) and recognizing RIF as a screening condition rather than a definite diagnosis. Physicians should keep in mind that the clinical uncertainty surrounding RIF is potentially risky because affected couples are vulnerable.

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Declaration

The authors report no financial or commercial conflicts of interest.

Figure 1: Relationship between pregnancy rate and rate of repeated implantation failure (RIF). According to the basal assumptions of the model, the prevalence of RIF and the chance of pregnancy in the no-RIF population were constant and set at 10% and 30%, respectively. The upper panel shows the chances of pregnancy per cycle according to the number of attempts. The lower panel illustrated the cumulative chances of pregnancy with the number of attempts.

Figure 2: Results from the two sensitivity analyses on the rate of IVF success and on the prevalence of repeated implantation failure (RIF). Five different rates were assessed for the two considered variables. In the upper panel, the rate of success of IVF was modified from 10% to 50%. In the lower panel the prevalence of RIF was modified from 5 to 25%. CPR, clinial pregnancy rate; ICSI, intracytoplasmic sperm injection.

Comment [S3]: Typesetter: please insert en rule between false and positive; change hyphen between IVF and ICSI to en rule; insert spaces either side of an equal sign;

Table 1. Possible causes and treatments of repeated implantation failure.[a]

Cause	*Causal relation*	*Diagnosis*	*Therapy*	*Therapy effective for RIF*	Main publications[b]
Lifestyle factors					
Smoking	Plausible	Anamnesis	Stop smoking	Plausible	Practice Committee of ASRM, 2012
Obesity	Debated	Weight and height	Weight loss	Debated	Practice Committee of ASRM, 2015
Gamete quality					
Oocyte	Plausible	None	Oocyte donation	Yes	Crawford and Steiner , 2015
Spermatozoa	Plausible	DNA Fragmentation	Testicular-epididymal extraction	Debated	Zini *et al*., 2017
Uterine factors					
Septate uterus	Plausible	2D/3D-US	Hysteroscopy	Debated	Practice Committee of ASRM, 2016
Endometrial polyps	Plausible	2D/3D-US or SIS	Hysteroscopy	Yes	Bosteels *et al*., 2015
Submucosal fibroids	Plausible	2D/3D-US or SIS	Hysteroscopy	Yes	Bosteels *et al*., 2015
Intramural fibroids	Debated	2D-US	Laparoscopy/laparotomy	Debated	Brady et al., 2013
Intrauterine adhesions	Debated	SIS	Hysteroscopy	Debated	Bosteels *et al*., 2015
Adenomyosis	Debated	2D/3D-US	Progestins or GnRHa	Debated	de Ziegler *et al*., 2016
Molecular alterations	Debated	None	Endometrial scratching	Debated	Ko and Ng, 2016
Adnexal pathologies					
Hydrosalpinx	Plausible	2D-US or HyCoSy	Laparoscopy (salpingectomy)	Yes	Johnson *et al*., 2010
Endometriosis	Debated	2D-US	Laparoscopy	Debated	Vercellini *et al*., 2014
Other					
Thrombophylia	Debated	Blood tests	Aspirin-heparin	No	Ata and Urman, 2016
Immunological factor	Debated	None	Corticosteroids, IVIG	Debated	Li *et al*., 2013; Robertson *et al*., 2016

[a]A tentative list of causes and treatments associated with a global judgment of the available evidence. For more in-depth systematic reviews, see Simon and Laufer (2012), Coughlan *et al*. (2014a), Zohni *et al*. (2016) and de Ziegler *et al*. (2016).
[b]If available, reviews were preferred.
2D-US, two dimensional ultrasound; 3D-US: three dimensional ultrasound; GnRHa, Gonadotrophin-releasing hormone agonist; HyCoSy, hystero-salpingo contrast sonography; IVIG, intravenous immunoglobulin; RIF, repeated implantation failure; SIS, saline infusion sonography.

Figure 1.

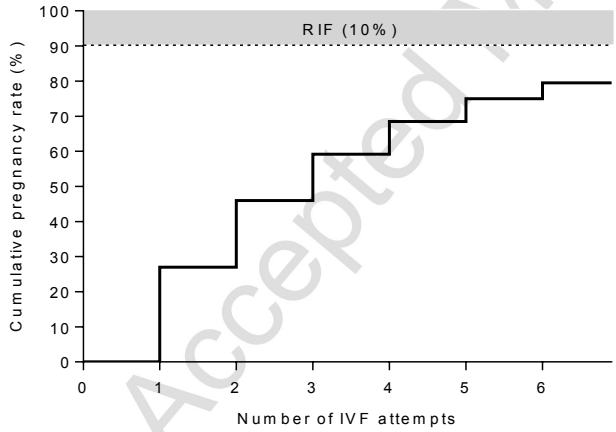

Figure 2.