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Defining Recurrent Implantation Failure: a profusion of confusion or simply an illusion?

Audrey S. Garneau, MD, **Steven L. Young, MD, PhD**

Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine (CB#7570), Chapel Hill, NC 27599-7570

Abstract

Recurrent implantation failure (RIF) is a poorly defined clinical scenario marked by failure to achieve pregnancy after multiple embryo transfers. The causes and definitions of implantation failure are heterogenous, posing limitations on study design as well as the interpretation and application of findings. Recent studies suggest a novel, personalized approach to defining RIF. Here, we will review implantation physiology and the definitions of implantation rate, failure, and RIF.

Capsule

Current definitions of RIF vary greatly. Future approaches to defining RIF may be personalized based on the presence or absence of risk factors for implantation failure, such as euploidy.

Keywords

Recurrent implantation failure; definition

Introduction

The implantation of an embryo is fundamental to a successful pregnancy. It is contingent on the presence of a specific intrauterine environment, a biologically intact embryo, and a complex series of interactions between them. This process, necessary for species survival, must be strongly influenced by natural selection but is curiously inefficient; most intercourse does not result in a fertilized egg, and only a fraction of fertilized eggs can become a baby. Even with an apparently euploid embryo, a large determinant of successful conception, embryo transfer results in ongoing pregnancy less than 60% of the time (1). Early abnormalities in implantation contribute to infertility by causing biochemical and first trimester losses, while later abnormalities are associated with pregnancy complications, such as miscarriage and preeclampsia (2).

audrey_garneau@med.unc.edu .

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Recurrent implantation failure (RIF) is a poorly defined but devastating clinical scenario where pregnancy is not achieved after multiple embryo transfers. However, there is a profound lack of agreement about the definition of RIF, and even some heterogeneity for the clinical determination of implantation and its failure. A standard definition of RIF would benefit the field by improving research study design and allowing the synthesis of independent studies. The data, thus created, would enhance our ability to determine specific causes, methods of diagnosis, and methods of treating and preventing RIF. The goal of this review is to make progress toward a universally accepted definition of RIF by exploring what is known about implantation and its failure.

What is implantation?

Early implantation and pregnancy

To understand failure of implantation, factors necessary for implantation need to be determined. The endometrium is receptive to implantation during a few days of the menstrual cycle, a window dependent on adequate progesterone exposure and endometrial response (3, 4). Steroid action and complex molecular and cellular crosstalk between the blastocyst and the endometrium are necessary for blastocyst apposition, attachment, and invasion (2, 5).

The temporal window of endometrial receptivity occurs at the peak of progesterone production by the corpus luteum. The effects of the weeklong exposure to sufficient progesterone are marked by maximal secretory changes, spiral artery formation, edema, and epithelial surface changes including pinopod formation (6). Clinical evidence of implantation can be obtained by the presence of hCG in the maternal blood. Although cleavage stage embryos at post-ovulatory day 3 (POD 3) express hCG mRNA, hCG does not enter the maternal circulation in clinically detectable amounts until trophoblast invasion and proliferation, POD 10–11 (5). Three weeks after ovulation, there is evidence of a gestational sac on ultrasound, and subsequently, ultrasound evidence of cardiac motion can reliably be detected 4.5 weeks after ovulation.

Later implantation abnormalities

Abnormalities of implantation can occur over a spectrum of time, and it is likely that abnormal implantation commonly underlies preeclampsia, IUGR, and pregnancy loss. For example, preeclampsia is strongly associated with shallow trophoblast invasion, deficient replacement of spiral artery endothelium by extravillous cytotrophoblasts, and alterations in blood flow leading to later manifestation of clinical disease (2, 6). Given the association of recurrent pregnancy loss and pregnancy complications, it might be useful to examine the association between RIF and those complications. To our knowledge, however, no studies have specifically examined such an association.

What are the causes of implantation failure?

Broadly, the causes of implantation failure may be categorized as embryonic, maternal, and endometrial:embryonic dyssynchrony.

Embryonic causes

The chromosomal quality of an embryo impacts the ability of the embryo to implant successfully. Euploid embryos, regardless of age, have been shown to have significantly lower implantation failure rates, 18–27%, compared to aneuploid embryos, 60–76% (7). However, transferring a euploid embryo does not preclude implantation failure; one study noted a 19–33% implantation failure rate, depending on the diagnostic definition of implantation failure (8).

Outside of chromosomal euploidy, gene mutations and alterations in methylation have an uncertain impact on recurrent implantation failure. Specific gene mutations resulting in loss or deficiency of endometrial factors, including cytokines and transcription factors, have been associated with implantation failure in mice (9, 10). While these discoveries help elucidate the complex molecular processes necessary for successful implantation, these mutations have not been identified in humans. Additionally, naturally occurring mutations causing implantation failure in mice have not been described, likely due to natural selection. Epigenetic changes in the embryo may also impact implantation(11). DNA methylation changes are essential in early embryo development, and methylation alterations have been found in embryos created from patients with long-standing infertility, though a causal relationship remains uncertain (12).

Maternal factors

Several maternal factors may also play a role in embryo implantation. While more recent studies have called into question the impact of endometrial thickness on live birth, it is impossible to ignore the data that strongly correlate pregnancy rate with endometrial thickness (13, 14). The available evidence supports that pregnancy rate is strongly influenced by endometrial thickness seen on day of hCG. In addition to endometrial thickness, cellular and molecular alterations of the endometrium are critical for implantation. Studies have shown that there is a tight window, perhaps two days, during which normal implantation occurs (4).

Maternal age and associated embryonic euploidy are of critical importance to embryonic implantation. Pirtea et al. showed that the implantation rate of single euploid embryos is 70%, 60%, 60% in subsequent transfers, with cumulative implantation of 70%, 88%, and 95% (15). The authors used this data to call into question whether there are a significant number of patients who have persistent problems with implantation (15). However, the population studied was particularly one of good prognosis, with a mean age of 35, AMH of 3 ng/mL, and BMI of 25 kg/m^2, and had a high dropout rate between transfers that could obscure a reduction in rates as transfer numbers increased. Other studies show that women with multiple implantation failures have a lower chance of future success. For example, an observational study of 118 patients with RIF found that 49% of these patients had a live birth in a 5.5-year follow-up period; however, approximately 50% of RIF patients did not realize their family goals (16). Another recent observational study found that women receiving a euploid embryo transfer were less likely to have a live birth if they had a history of greater than two implantation failures, 36% compared to 47% in those without this reproductive history (17).

There are other specific maternal causes of implantation failure to consider, though many are arguably exclusion criteria for the diagnosis of RIF. Examples of such scenarios include inflammatory states associated with communicating hydrosalpinx and chronic endometritis. The impact of hydrosalpinges has been well documented in multiple RCTs, and chronic endometritis has been associated with a 3-fold decrease in implantation rates (18, 19). Intracavitary lesions such as submucosal myomas and endometrial polyps also increase the odds of implantation failure (20–22). Endometriosis may also cause implantation failure, as studies show that treatment of endometriosis either by GnRH agonist or surgical management improves outcomes (23, 24). There are many additional possible etiologies for RIF, including antiphospholipid antibody syndrome, PCOS, obesity, and smoking, though many causes remain unexplained. Lesser defined causes may involve specific haplotypes or additional immunological causes. A comprehensive description of these causes is beyond the scope of this review.

Endometrial:Embryonic Dyssynchrony

Dyssynchrony between endometrial and embryonic development may also play a role in the failure of implantation. The length of progesterone exposure in the uterus is critical, though assessment of this is difficult (4). Testing for the displacement of the window of implantation by endometrial receptivity assay has emerged as a possible way to evaluate receptiveness of the endometrium; data remains controversial as to whether this is beneficial in patients who experience RIF (25, 26). However, the molecular mechanisms underlying the action of estrogen and progesterone-induced cellular changes and bidirectional communication with the embryo cannot be overlooked. These intricate steps likely offer an opportunity for error not otherwise clinically relevant or testable.

How is implantation rate defined?

To define implantation failure, it is necessary to first define successful implantation and implantation rate. Currently, there are several different ways to determine the implantation rate. An obvious approach is to use serum hCG as a surrogate for trophoblast invasion. Data reported to SART measures implantation rate as number of gestational sacs/number of embryos transferred, as this allows a definition based on the number that implanted per number transferred. However, the SART definition cannot account for embryos that were implanted but lost before ultrasound. An additional definition used in some studies is the sustained implantation rate, which is the number of embryos with cardiac activity per number of embryos transferred. The sustained implantation rate is useful clinically as it tracks closely with live birth. With each of these definitions, the absence of the appropriate finding (hCG, sac, cardiac motion) represents a failed treatment cycle, though it remains unclear whether failure at each of these points have the same or similar causes. For example, biochemical losses seem to occur with similar frequency with aneuploid and euploid embryos, while failure to achieve detectable hCG is about half as likely for aneuploid embryos (7). It would seem useful to track all three definitions, at least in research, and report on all three until a universal definition is applied.

It is important to note that a distinction, or lack thereof, between miscarriage and implantation failure is needed. Clearly from a reproductive outcome and treatment perspective, but also given the adverse perinatal outcomes associated with recurrent miscarriage (27). Additionally, there may be long term impact of recurrent loss, such as increased risk of myocardial infarction, that may warrant specific screening in patients at high risk (28).

What is recurrent implantation failure?

Once a definition of implantation is determined, the definition of its failure is obvious. Yet, how we define recurrent remains unclear. The aim of a definition of RIF should be to identify those women who have an abnormally low chance of pregnancy per embryo, in order to provide prognostic data and allow interventions that may improve implantation in subsequent transfers. Currently, there is heterogeneity in criteria deemed indicative of RIF between types of providers, clinics, and geographic location. A recent international survey of 735 clinicians highlights the heterogeneity of currently-used clinical criteria [27]. In this survey, 84% of clinicians defined RIF based on the number of embryos transferred, with the majority (45%) defining RIF as failure of three fresh or frozen embryo transfers. Interestingly, factors such as location of the clinic (European versus non-European) and private versus public were correlated with the definition used (29).

Individual authors have proposed specific definitions. Tan et. al suggested a definition of failure to achieve a pregnancy after 3 completed IVF cycles (30). Two additional studies defined RIF as 3 unsuccessful cycles of IVF with at least 2 embryos of high quality or failure of clinic pregnancy after 4 good quality embryo transfers with at least 3 fresh or frozen IVF cycles in women under the age of 40 (31, 32). There is also variation in how professional societies define RIF. The preimplantation genetic diagnosis consortium of the European Society of Human Reproduction and Embryology PGD Consortium (33) has defined RIF as >3 failed embryo transfers with high quality embryos, or the failed transfer of ≥10 embryos in multiple transfers (3, 10, 16, 34). ASRM has not published specific criteria.

A critical problem with these definitions is that there are many important factors influencing implantation success are not accounted for, including oocyte and uterine age, length of infertility, euploidy (and how this was determined), systemic diseases, lifestyle issues (e.g. obesity or smoking), uterine structural abnormalities, chronic endometritis, and presence of endometriosis. Some of these are routinely screened for and others are not, but might be if RIF is diagnosed. Obviously, the lack of implantation of a high-quality blastocyst in a 28 year old woman with absent tubes as her only infertility factor would be much less likely than a 39 year old with transfer of untested, cleavage-stage embryos. Thus, recently, authors have suggested personalized definitions of implantation failure. Embryo aneuploidy (and therefore oocyte age) is arguably the most important contributing factor to failure of ART. For this reason, Ata et al. proposed a new definition of RIF that accounts for anticipated euploidy rate on the basis of age, using a statistical model (34). The statistical simulation found that no age category was associated with a 95% probably of successful implantation with six embryos transferred! Rather, a 95% probability of success was not reached until seven blastocysts were transferred in women < 35 years old. The needed number of embryos

increased with age; at 38 years of age, 10 blastocysts were needed, and at age 42 there was no practical number that allowed a 95% probability of implantation. Of course, the number needed would be reduced, if euploid embryos are transferred. Rozen et al. suggested using a theoretical implantation rate (TIR) to create a personalized diagnosis of RIF and to account for many of the aforementioned factors, but the authors did not provide a way to calculate the TIR, and large scale data taking all of these factors into account is lacking (35).

Conclusion

In conclusion, RIF does not have a universal definition. Clinical experience tells us that some women have a greatly reduced chance of embryo implantation. These women, if they possess an adequate supply of euploid oocytes, often are able to conceive with further IVF attempts, since the chances are seldom 0%. However, the emotional and financial burdens of these choices are high and the chance of success is certainly not optimal. Therefore, a practical definition of RIF is needed to inform both research and clinical practice. We propose that large scale data be applied to allow personalization of the diagnosis by modeling multiple factors. Until we have the ability to more fully personalize, definitions should at minimum account for the risk of aneuploidy as a significant factor governing implantation.

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