

# Recurrent Implantation Failure



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Recurrent Implantation Failure (RIF) has been defined as “the scenario in which the transfer of embryos presumably viable has failed to result in a positive pregnancy test sufficiently often in a specific patient to warrant consideration of further investigations and/or interventions” by the ESHRE Working Group on RIF in January 2023. RIF can be observed only in couples undergoing IVF. “The recommended threshold for RIF is 60%, meaning that couples who have not had a successful implantation despite an estimated cumulative chance of implantation to date of at least 60% should be counselled on further investigation and/or treatment options”.

The three stages of a failed IVF cycle include:  
1) Completely failed IVF with a negative hCG;  
2) Failure after there is a positive hCG but no pregnancy is ever identified on ultrasound; and  
3) Pregnancy Loss where a clinical pregnancy is detected and then fails. ESHRE defines successful implantation as the achievement of a positive pregnancy test (i.e., detection of beta hCG in serum or urine, or ultrasonographic visualization of one or more gestational sacs with fetal heartbeat) following an embryo transfer procedure. For our patients, and to many clinicians, these three distinct outcomes are considered the same as there is not an ongoing pregnancy.

In order for successful implantation to occur there needs to be a *receptive endometrium*, a *competent embryo*, and *communication* between embryonic and maternal tissue. Implantation

involves three stages. The first stage is *apposition*, which is the unstable attachment of a blastocyst to the endometrial surface. The second stage is *adhesion*, which is a more stable attachment of the trophoblast to the luminal epithelium. Finally, the *invasion* stage involves trophoblastic directed growth into the maternal vasculature. For these processes to be successful, there must be continued “cross-talk” between the maternal and fetal tissue. Based primarily on studies with the use of donor oocytes in older women, it has been stated that when considering implantation, 75% is related to the embryo and 25% is related to the endometrium.

Attention was originally focused primarily on the embryo and many thought that preimplantation genetic testing (PGT) would resolve the majority of cases of RIF. As the use of PGT has expanded and the cases of RIF have grown, attention has recently started to focus more on the uterine environment. We must be sure that visible abnormalities, detected by 3D saline infusion sonography looking for congenital and acquired uterine anomalies, are corrected when appropriate. Chronic endometritis should be tested for and treated. Blood levels of TSH, Vitamin D, Progesterone, and hemoglobin A1c to evaluate hormonal imbalances should be corrected. Newer but unproven molecular technologies such as the endometrial receptivity assay (ERA, EMMA, ALICE) and the Receptiva Dx (BCL6, beta3 Integrin, CD138+) are being used in the absence of good clinical data. More endometrial tests will follow.

Lifestyle factors such as obesity, tobacco use, alcohol use, and excess caffeine use can all adversely affect implantation and are often overlooked. Laboratory factors related to embryo growth and development as well as physician factors can also play important roles in reducing successful implantation. Each clinic should develop a strategy to evaluate causes of implantation failure, keeping in mind that the source of the oocytes and sperm is a significant factor. Almost 70% of clinicians consider oocyte or sperm donation a treatment option in RIF.