Recurrent Implantation Failure

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Recurrent Implantation Failure (RIF) has been defined as the failure of a clinical pregnancy after four good quality embryos have been transferred in a minimum of three fresh or frozen IVF cycles in women under the age of 40. For women using donor oocytes, the threshold to be diagnosed with RIF drops to four good quality embryos after two embryo transfers cycles. RIF is only applicable to couples undergoing IVF. The three stages of a failed IVF cycle include: 1) Completely failed IVF with a negative hCG; 2) Implantation failure where 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. For patients, and for many clinicians, these three distinct outcomes are incorrectly considered the same, as there is not 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.

There are no official guidelines for the evaluation of RIF from ASRM or ESHRE. 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 sonohysterography or hysterosalpinography, looking for congenital and acquired uterine anomalies, are corrected when appropriate. But newer molecular technologies such as the endometrial receptivity assay (ERA, EMMA, ALICE) and the Receptiva Dx (BCL6, beta3 Integrin, CD138+) are becoming more important. More endometrial tests will follow. Blood levels of prolactin, TSH, and hemoglobin A1c to evaluate hormonal imbalances should be corrected.

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.