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What is recurrent implantation failure?

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INTRODUCTION

Successful implantation

Implantation is a complex phenomenon, still not thoroughly understood, involving the embryo and the endometrium.[1] Implantation has been considered as a gradual process requiring embryo adhesion to the luminal surface of the endometrium, followed by invasion of the trophectoderm cells from the embryo, through the luminal epithelium, into the deeper layer of the endometrium.[2,3] These complex molecular interactions between the uterus and the mature blastocyst are necessary to establish the uteroplacental circulation and finally lead to implantation, approximately six or seven days after fertilization.[1,4] By the 10th day after fertilization, the blastocyst is completely embedded in the stromal tissue of the uterus, leading to cytotrophoblast invasion into the entire endometrium and the inner third of the myometrium, as well as the uterine vasculature.[5]

In clinical practice, implantation can be confirmed by a rising human chorionic gonadotrophin (hCG) level, which occurs eight to ten days after ovulation or 14 days after oocyte retrieval

in assisted reproductive technology (ART) cycles.[6] It is considered to be successful when there is ultrasonographic evidence of an intrauterine gestational sac after five weeks of gestation, or usually three weeks after oocyte retrieval in ART cycles.[2]

Unfortunately, pregnancy achievement in the human is a relatively inefficient process, with a probability of conception approximately 25%–30% per cycle.[7] Thus, it is more likely for a human embryo not to implant than to lead to establishment of pregnancy.[1]

Implantation failure

From a clinical point of view, implantation failure may occur very early during the adhesion stage, with no detectable hCG production and, thus, no objective evidence of pregnancy. It may also occur at a later stage, after initiation of hCG production from the implanting embryo, without, however, formation of an intrauterine gestational sac visible on ultrasonography, which is clinically recognized as biochemical pregnancy.[2,3]

Implantation failure may be due to embryo and/or maternal factors. Problems due to the embryo can be associated either with poor oocyte quality or with paternal factors.[8] On the other hand, implantation problems associated with the female may be due to uterine, tubal, or immunological factors; endometriosis; or thrombophilia.[9,10] Surprisingly, the high implantation rate of donated oocytes in women of advanced reproductive age suggests that oocyte quality rather than endometrial receptivity largely determines the success of implantation.[1,11]

In non-oocyte donation cycles and despite the technological advances in *in vitro* fertilization (IVF),[3] only about one-quarter of IVF cycles will result in live births, leading many couples to experience multiple IVF failures. After each failed IVF attempt,

pregnancy rates decrease significantly in subsequent cycles, with the most remarkable decrease after the third cycle.[12] Failure to achieve pregnancy after multiple IVF attempts is recognized as recurrent implantation failure (RIF).[2]

FACTORS CONTRIBUTING TO RIF

The embryo

The embryo has been implicated in RIF in the presence of poor oocyte or spermatozoa quality. Poor oocyte quality has been associated with advanced maternal age, known to lead to a low number of oocytes that are usually aneuploid.[13] On the other hand, poor spermatozoa quality has been associated with sperm DNA damage, also leading to the formation of poor-quality embryos.[14]

Uterine pathologies and endometrial receptivity

A number of congenital uterine abnormalities, including Müllerian-duct malformations as well as submucous fibroids, endometrial polyps, intrauterine adhesions, or adenomyosis, may seriously affect endometrial receptivity and contribute to RIF.[15,16] A functioning and receptive endometrium is of crucial importance for successful embryo implantation. Endometrial receptivity refers to the synchronized interaction among ovarian hormones, growth factors, adhesion molecules, cytokines, and lipids, allowing embryo adhesion, invasion, placentation, and therefore pregnancy initiation to occur.[9,17] Impaired endometrial receptivity is responsible for approximately two-thirds of implantation failures.[18]

Whether or not a thin endometrium is associated with impaired endometrial receptivity is still a matter of debate.[19] The minimal adequate endometrial thickness for successful

implantation varies between studies, ranging from 6–8 mm.[20,21] Significantly higher embryo implantation and pregnancy rates have been demonstrated in patients with an endometrial thickness of >9 mm compared with those with a thickness <9 mm.[22–24] On the other hand, two large prospective studies failed to confirm such an association.[25,26]

Hydrosalpinges

Hydrosalpinges have also been recognized as a contributing factor to RIF due to their harmful impact on implantation. Hydrosalpinges may negatively influence implantation either by a direct toxic effect on the preimplantation embryo or mechanically by flushing the embryo out of the uterus. Moreover, it has been shown that endometrial receptivity is impaired in the presence of hydrosalpinges due to the abnormal expression of cytokines, which are necessary for successful implantation.[27,28]

Immunological factors/thrombophilia

Endometrial decidualization is a process in which the differentiation of endometrial stromal cells occurs. It is of vital importance for pregnancy establishment and maintenance, enabling maternal immune tolerance, fetus survival, and placentation process regulation.[29] In this respect, the impact of various immunological factors on implantation has attracted a lot of attention as a cause of RIF, although no consensus exists on whether or not immunological investigations and treatments may be beneficial.[2,30]

The role of thrombophilia in implantation failure has been also the focus of research.[31–33] The association of inherited thrombophilia, antiphospholipid or other autoantibodies, with

RIF has been investigated with, however, controversial results.[34,35] Hence, the value of thrombophilia screening in patients with RIF still remains a matter of debate.

VARIABLES USED IN THE DEFINITION OF RIF

Quality and number of embryos transferred

Generally, the probability of an embryo to implant is 30%, and thus, in order to increase the probability of pregnancy, it is imperative that the best-quality available embryo(s) are selected for transfer. A good-quality embryo has been defined as an embryo with the number of cells corresponding to the day of its development, blastomeres of equal size with regular distribution, and less than 10% fragmentation.[36] In addition, day-5 embryos (blastocysts) have been graded according to the expansion and quality of the inner cell mass and the trophectoderm.[36]

Due to the higher implantation potential of a blastocyst compared with that of a cleavage-stage embryo, the developmental stage of the embryo transferred has also been taken into account in the definition of RIF.[2,37] Single-blastocyst transfer has been suggested to result in a similar probability of live birth compared to the transfer of two cleavage-stage embryos.[38–41]

Several definitions of RIF have been proposed including various numbers of embryos transferred per cycle or a cumulative number of embryos transferred overall. Controversy exists regarding the inclusion or not of frozen embryos in the number of total embryos used to define RIF. It has been suggested that frozen embryos should not be included in the definition of RIF due to their lower implantation rate compared with fresh embryos.[42] However, the opposite has also been suggested since transfer of frozen embryos contributes to the

cumulative pregnancy rate achieved.[43–45]

Number of unsuccessful IVF/ICSI cycles

Many investigators have preferred to base the definition of RIF on the number of unsuccessful IVF/intracytoplasmic sperm injection (ICSI) cycles alone using different numbers, ranging from one to multiple cycles, usually in combination with other variables.

Maternal age

Maternal age has been incorporated into the definition of RIF, given the fact that maternal age is closely related to embryo quality.[46] It has been demonstrated that implantation rates remain constant until the age of 35, followed by a linear decrease of 2.77% per year.[47] Moreover, it has been shown that aneuploidy significantly increases with maternal age, and thus, implantation failure in women of advanced maternal age may be largely attributed to this problem.[48] Although the age limit of 40 years has been proposed as an upper age limit for defining RIF in combination with other factors,[2] it still has not been widely adopted.

DEFINITION OF RIF

As already discussed, many variables have been used for the definition of RIF, including number of embryos transferred, number of IVF attempts, embryo quality, or maternal age.[7] Using these variables in different combinations, several definitions of RIF have been proposed without, unfortunately, a universally accepted definition being present. Consequently, the exact prevalence of patients with RIF is difficult to be determined.

According to an early definition, dated more than 20 years ago,