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REVIEW

What exactly do we mean by ‘recurrent implantation failure’? A systematic review and opinion




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Abstract Recurrent implantation failure (RIF) is an iatrogenic condition, being the result of repetitive unsuccessful cycles of IVF or intracytoplasmic sperm injection (ICSI) treatment. The aim of this review was to assess the definitions of RIF used in literature as well as suggest a uniform definition of this condition. A systematic search of MEDLINE, Embase and Cochrane Library was conducted. The most commonly stated definitions described RIF as ‘three or more failed treatment cycles’ or ‘two or more failed cycles’. Other identified definitions were based solely on the number of embryos transferred in previous cycles or combined the number of previously failed cycles with the number of transferred embryos. Several other definitions were also identified. This review highlights the lack of uniformity of the definition of RIF. Based on the available literature and the expert opinion of the authors, RIF should be defined as the absence of implantation after two consecutive cycles of IVF, ICSI or frozen embryo replacement cycles where the cumulative number of transferred embryos was no less than four for cleavage-stage embryos and no less than two for blastocysts, with all embryos being of good quality and of appropriate developmental stage. 

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Introduction

Human reproduction is a relatively ineffective process, with only 20–25% of apparently fertile couples becoming

pregnant during a single menstrual cycle assuming tubal patency, ovulation and viable spermatozoa (Short, 1979; Stevens, 1997). Based on this generally accepted level of fecundity, the likelihood of achieving pregnancy has been

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estimated at 74%, 93% and 100% after 6, 12 and 24 months, respectively of unprotected, regular intercourse (Evers, 2002; Teklenburg et al., 2010).

Events leading to a successful pregnancy commence with fertilization of the oocyte. Research suggests that the early embryo undergoes the same stages of implantation as an activated, migrating leukocyte when transgressing vascular endothelium: namely, rolling, apposition, adhesion and invasion (Genbacev et al., 2003). Taking this model into consideration, implantation should be considered only until the invasion of the embryo is complete and the latter is formally embedded within the endometrium. This phase will be heralded by an increase in serum human chorionic gonadotrophin (HCG) concentrations. In-vitro studies confirm secretion of the β subunit of HCG by the developing embryo 7 days after fertilization (Dokras et al., 1991; Marshall et al., 1968; Woodward et al., 1993). It is unclear, however, at what time point implantation can be formally confirmed and, by default therefore, when implantation failure can be diagnosed. This is obviously a contentious issue but an important one at least as far as semantics are concerned. The ability to unequivocally state when implantation occurred, would allow differentiation between the failure of implantation and miscarriage. These clinically distinct entities are often confused and in combination are collectively referred to as 'recurrent reproductive failure', which suggests that they are different manifestations of the same underlying problem (Farquharson et al., 2005). This is not a universal view, however, and yet many couples with recurrent implantation failure are investigated and managed in a similar, if not identical, way to those with recurrent miscarriage (Christiansen et al., 2006).

The pressures of society, modern lifestyles and changes within the environment all combine to make it more difficult for couples to start a family, and subfertility appears to be becoming more common with a current, estimated prevalence of 10–15% (Evers, 2002; Shreeve and Sadek, 2012). Since the introduction of IVF in the 1980s, some couples that may have otherwise remained childless have had an opportunity to become parents. Assisted reproduction treatment is, however, no more efficient, and possibly less effective, than normal human reproduction, with implantation rates consistently in the region of 20–30% (Voullaire et al., 2002). Life table analyses of cumulative pregnancy rates following multiple cycles of IVF have shown that assisted reproduction treatment is not the panacea it was once proposed to be and that a proportion of couples remain childless despite multiple cycles of treatment. Cumulative pregnancy rates after treatment have been estimated to be 40–55% after three IVF cycles (Guzick et al., 1986; Roest et al., 1998; Simon et al., 1993) and 51–75% after six consecutive cycles (Alsalili et al., 1995; Dor et al., 1996; Guzick et al., 1986; Simon et al., 1993). Cumulative pregnancy rates do not significantly increase thereafter, and pregnancy rates per cycle tend to fall after the third unsuccessful treatment (Croucher et al., 1998; Osmanagaoglu et al., 1999; Sharma et al., 2002). Mathematical modelling has also demonstrated a steady decrease in live birth following a failed IVF cycle. A 50% reduction in live birth was noted after the 10th failed cycle for double-embryo transfers and lower rates were associated with single-embryo transfer (Roberts and Stylianou, 2012;

Roberts et al., 2010, 2011). Failure to conceive after repeated attempts of treatment is often referred to as 'recurrent implantation failure' (RIF). However, the exact definition of this entity remains unclear and current descriptions incorporate the number of previously failed cycles and whether these were fresh or frozen, the number of embryos transferred and/or their respective quality, or a combination of these factors.

This article provides an up-to-date overview of the definitions of RIF currently being used in the scientific literature. The aim is to clarify the terminology used and standardize the inclusion criteria in future studies of RIF to allow a more appropriate comparison between patient populations.

Materials and methods

Eligibility criteria

Inclusion criteria were any type of study where the definition of RIF in human subjects was used. Case reports and conference abstracts, if deemed appropriate, were included. Review articles and letters to the editor were excluded. There was no limitation on language, publication date or publication status. In cases where suitability for inclusion could not be ascertained after analysis of the abstract, the complete article was obtained. Reference lists from included articles were manually screened for articles that could have been missed during the initial search.

Information sources and search

The following databases were searched electronically: Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE) and Embase, spanning the years from 1946 to June 2013.

Search terms

The following search terms were used, adjusting for each database as necessary: recurrent implantation failure*, recurrent failure to implant, repeat failure to implant, implantation failure*, repeat* implantation failure, recurrent failed implantation, repeat failed implantation*, RIF, recurrent reproductive failure*, repeat reproductive failure, poor implantation, artificial reproductive treatment*, ART, in-vitro fertilization, IVF, intracytoplasmic sperm injection and ICSI. MESH terms were expanded appropriately to gain the maximum number of options.

Study selection

Two independent reviewers (LTP and MNB) screened the retrieved titles and abstracts selecting and excluding those that clearly did not meet the eligibility criteria; disagreements between reviewers were resolved by consensus or a third party (NRF). One author (LTP) obtained full articles of all potentially relevant studies, which were examined

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