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REVIEW

Recurrent implantation failure: definition and management

C Coughlan [a], W Ledger [b], Q Wang [c], Fenghua Liu [d], Aygul Demirol [e], Timur Gurgan [e], R Cutting [a], K Ong [f], H Sallam [g], TC Li [a,*]

[a] *Department of Reproductive and Developmental Medicine, Jessop Wing, Royal Hallamshire Hospital, Sheffield, United Kingdom;* [b] *Department of Obstetrics and Gynaecology, Royal Hospital for Women, Sydney, Australia;* [c] *Reproductive Centre, First Affiliated Hospital of Sun Yat Sen University, Guangzhou, China;* [d] *The Women and Children Hospital of Guangdong Province, No. 13, Guangyuan Road West, Guangzhou 510010, China;* [e] *Women's Health, Infertility and IVF Centre, Cankaya Caddesi, 20/3, Ankara, Turkey;* [f] *Monash IVF, Gold Coast, Australia;* [g] *Department of Obstetrics and Gynaecology, University of Alexandria and Suzanne Mubarak Regional Centre for Womens Health and Development, Alexandria, Egypt*

* Corresponding author. *E-mail address:* tin.li@sth.nhs.uk (TC Li).

Dr Carol Coughlan received her medical training in Ireland and obtained her MRCOG in 2003 and MRCPI in 2004. She completed subspecialist training in reproductive medicine and surgery at the Jessop Wing, Royal Hallamshire Hospital, Sheffield, UK. She is pursuing her research interests in recurrent implantation failure and recurrent miscarriage.

Abstract Recurrent implantation failure refers to failure to achieve a clinical pregnancy after transfer of at least four good-quality embryos in a minimum of three fresh or frozen cycles in a woman under the age of 40 years. The failure to implant may be a consequence of embryo or uterine factors. Thorough investigations should be carried out to ascertain whether there is any underlying cause of the condition. Ovarian function should be assessed by measurement of antral follicle count, FSH and anti-Müllerian hormone. Increased sperm DNA fragmentation may be a contributory cause. Various uterine pathology including fibroids, endometrial polyps, congenital anomalies and intrauterine adhesions should be excluded by ultrasonography and hysteroscopy. Hydrosalpinges are a recognized cause of implantation failure and should be excluded by hysterosalpingogram; if necessary, laparoscopy should be performed to confirm or refute the diagnosis. Treatment offered should be evidence based, aimed at improving embryo quality or endometrial receptivity. Gamete donation or surrogacy may be necessary if there is no realistic chance of success with further IVF attempts.

KEYWORDS: failure, implantation, IVF, fibroids, hysterosalpingogram, embryo

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Introduction

Implantation is a process whereby the embryo attaches itself to the luminal surface of the endometrium followed by migration via the luminal epithelium and invasion into the deep layer of the endometrium to become embedded into the deeper layer (Figure 1). Traditionally, implantation has been considered as a process involving only the embryo and the endometrium, but recent studies show that cumulus cell competency may also contribute to the process (Benkhalifa et al., 2012). While implantation is a process with a well-defined starting point, it is a gradual process which lasts for several weeks with no universal agreement on when the process is completed.

In clinical practice, implantation is often considered to be successful when there is ultrasonographic evidence of an intrauterine gestational sac. Conversely, implantation failure is considered to have occurred if there is a lack of ultrasonographic evidence of an intrauterine gestational sac. Implantation failure may occur very early on during the attachment or migration stages, with the result that there is no objective evidence of a pregnancy, i.e. negative urine or blood pregnancy test (human chorionic gonadotrophin, HCG). It may also occur later on, following successful migration of the embryo through the luminal surface of the endometrium, when HCG produced by the embryo may be detected in the blood or urine, but the process becomes disrupted prior to the formation of an intrauterine gestational sac. In this situation, it is clinically referred to as a biochemical pregnancy. In assisted conception treatment, implantation is considered to be successful when an embryo has produced an intrauterine gestational sac, detectable by ultrasonography, usually about 3 weeks after oocyte retrieval or about 5 weeks of gestation.

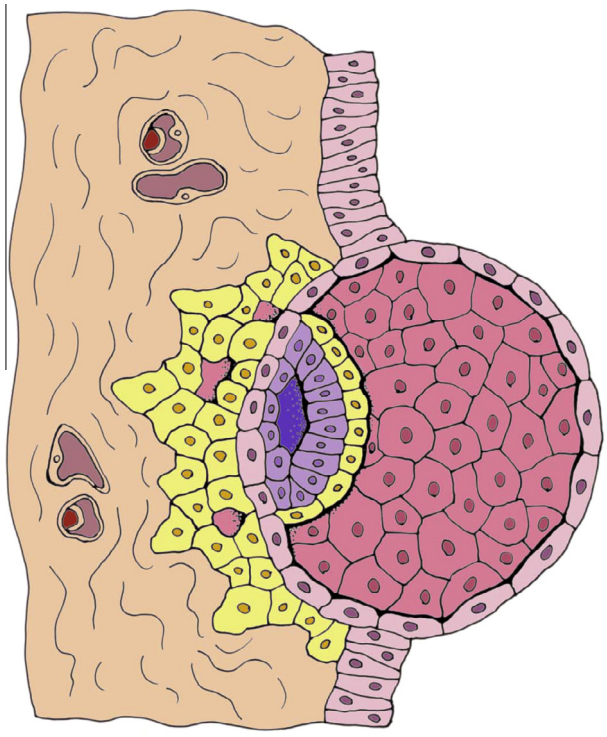

Figure 1 The initial stage of implantation, when the embryo is invading the epithelial layer of the endometrium to be embedded in the stroma compartment.

The implantation rate is defined as the number of embryos which have produced ultrasonographic evidence of an intrauterine gestational sac per the total number of embryos transferred into the uterine cavity (Zegers-Hochschild et al., 2009). In IVF—embryo transfer cycles, the implantation rate when day-2 or -3 embryos are transferred is about 25%, but the implantation rate when day-5 or -6 embryos are transferred is usually higher, about 40%.

Implantation failure refers to the failure of the embryo to reach a stage when an intrauterine gestational sac is recognized by ultrasonography. From the clinical point of view, it is worthy to note that the term 'implantation failure' refers to two different types of situation, those in whom there has never been evidence of implantation (no detectable HCG production) and those who have evidence of implantation (detectable HCG production) but it did not proceed to beyond the formation of a gestational sac visible on ultrasonography. Implantation failure may be a consequence of embryo or endometrial factors.

Definition of recurrent implantation failure

Recurrent implantation failure (RIF) is a clinical entity which refers to a situation when implantation has repeatedly failed to reach a stage recognizable by pelvic ultrasonography. There is as yet no universally accepted definition for RIF, despite many publications on this topic (Das and Holzer, 2012; Laufer and Simon, 2012; Penzias, 2012; Simon and Laufer, 2012a,b; Urman et al., 2005).

Because the probability for an embryo to successfully implant is only approximately 30%, the probability of it failing to implant is approximately 70%. However, following transfer of two embryos, the probability of both embryos failing to implant is $0.70^2 = 0.49$. Following the replacement of 3, 4, 5 or 6 embryos, the probabilities of all embryos failing to implant becomes $0.70^3 = 0.34$, $0.70^4 = 0.24$, $0.70^5 = 0.17$ and $0.70^6 = 0.12$, respectively. In a clinical setting, one has to decide when it becomes unusual for all transferred embryos to fail to implant. And then ask the question: why do all transferred embryos not implant?

The embryo

Quality

One important variable is clearly the quality of the embryo. If the quality of the embryo is poor, and assuming that the probability of successful implantation is reduced only to 0.10, following the transfer of 2, 3, 4, 5, 6 and 7 embryos, the probabilities of all embryos failing to implant is 0.81, 0.73, 0.66, 0.59, 0.53 and 0.48, respectively. In other words, there is still a 48% chance that all seven embryos will fail to implant. Hence, in arriving at a clinically useful definition, some investigators specified that good-quality embryos had been transferred (Margalioth et al., 2006). A good-quality embryo was defined as having the correct number of cells corresponding to the day of its development and day-5 embryos (blastocysts) were graded according to