REPEATED IMPLANTATION FAILURE

*Rif, Recurrent Implantation Failure*

The absence of implantation after three or more transfers of high quality embryos or after placement of 10 or more embryos in multiple transfers.

**Diagnosis**

- Female

**Related Diagnoses:**

- Thyroid disorders
- Autoimmune disorders
- Antiphospholipid syndrome
- Uterine malformations
- Lupus erythematosus

**About Repeated implantation failure**

Successful embryo implantation is a process which requires both a synchronous development and interaction between hatched blastocyst and endometrium. The process of implantation as a scheme is presented in Pic. 1, where the diagram shows a preimplantation stage of embryo and some important factors thought to be necessary for uterine receptivity: COX-2 (cyclooxygenase-2), EGF (epidermal growth factor) and LIF (leukemia inhibiting factor). From the clinical point of view, implantation is considered to be successful when gestational sac is diagnosed by ultrasound.

The term “implantation failure” refers to two different types of cases:

- 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.

**RIF has been defined as the absence of implantation after three or more**
transfers of high quality embryos or after placement of 10 or more embryos in multiple transfers (for more detailed definition according to different authors see Tab.1). Maternal factors may also contribute, and the clinical approach to investigating RIF now involves the exclusion of thrombophilic gene mutations, autoimmune conditions and uterine anomalies. However, in the majority of cases no clear cause can be identified. In recent years it has become apparent that constitutive endometrial dysfunction could represent an important contributor to this condition. The transition into a receptive uterus includes cellular changes in the endometrium and the modulated expression of different cytokines, growth factors, transcription factors, and prostaglandins. Embryo implantation is associated with an active Th1 inflammatory response while a Th2-humoral inflammation is required for pregnancy maintenance. Yet, the findings suggest that a Th1 inflammatory response is also necessary for the acquisition of uterine receptivity.

The causes of implantation failure are diverse and especially due to different maternal factors as uterine abnormalities, hormonal or metabolic disorders, infections, immunological factors, thrombophilias as well as other less common ones. Also it is essential to note the influence of severe male factor and its impact on genetic and morphological state of the embryo. Some recent studies investigated the role of many other factors in this complex process of implantation, such as contribution of cumulus cells.

In recent decades, many infertile couples, who otherwise would not have been able to have children, have benefited considerably from assisted reproductive technology (ART). However, despite the selection of morphologically good embryos for transfer, there are still some women who fail to become pregnant. Recently, the concept of recurrent implantation failure (RIF) has emerged because the implantation process remains the least understood step in ART. It is known that the success of embryo implantation depends primarily on the quality of the embryos transferred. Nonetheless, embryo quality alone cannot fully explain all cases of RIF, particularly in young women, whose embryos should be of good quality. It is believed that efforts to align criteria for definition of recurrent implantation failure (RIF) and attempts to classify different RIF types would develop guidelines for treatment procedures which would result in an increase in patients’ opportunities to conceive.

In some cases, RIF can be defined as a unique condition due to unidentified abnormalities or damage of the endometrium which would not even allow the initial steps of embryo implantation (apposition, attachment). If that is the case, the endometrium and its ability to provide, in a timely restricted manner, an environment suitable for embryo implantation should be regarded as a crucial factor. Nevertheless, another alternative would be the existence of a combined deficiency of both the embryo and the endometrium which would transform the cross-talk between the mother and the embryo in an ineffective or unsynchronized way. This would create a total blockade or disarrangement of the sophisticated cascade of molecular signaling needed in both embryo
and endometrium for successful implantation and pregnancy. Also it is essential to note the influence of severe male factor and its impact on genetic and morphological state of the embryo. Some recent studies investigated the role of many other factors in this complex process of implantation, such as contribution of cumulus cells.

Trying to summarize the above facts and causes of implantation failure, the following classification of RIF seems to be helpful which allows taking correct therapeutic approaches for these patients (Pic. 2).

I. Multifactorial RIF (wide variety of reasons for RIF):

- Maternal anatomic factors, including congenital uterine abnormalities, endometrial polyps, uterine fibroids, adhesions, hydrosalpinges, endometriosis, etc.
- Male factors, when severe oligoasthenozoo-spermia was diagnosed or increased sperm DNA fragmentation
- Genetic abnormalities, where embryos with good morphology have aneuploidy
- Hormonal or metabolic disorders (uncontrolled diabetes, thyroid disease, variations in the prolactin level, etc.)
- Infections
- Thrombophilias or antiphospholipid syndrome
- Immunological factors
- Psychological factors, lifestyle

II. Endometrial RIF (impaired endometrium): unsuccessful attempts with the transferring of high grade embryos, due to thin (≤6 mm) endometrium, with or without variations in vascularity.

III. Idiopathic RIF (impaired cross-talk between endometrium and embryo): unexplained failure to achieve pregnancy after ET of good quality embryos, without any anatomical and histological changes in uterine cavity and endometrium, without any other disturbances in patient, patient-partner and embryos.

Associated diseases

- endometritis
- polycystic ovaries
- thyroid disorders
- hydrosalpinx
- uterine and ovarian disorders
- endometrial polyps
- adhesions
- uterine septa

Complications
Infertility

Implantation failure, which is presently the major barrier in human fertility, is attributed, in many cases, to the failure of the uterus to acquire receptivity.

Risk factors
- thrombophilia
- anatomical malformations of the uterus
- immunological factors
- a non-functioning endometrial
- chronic uterine inflammation

Impact on fertility

Although several medical causes have been established, up to 50% of cases of recurrent pregnancy loss, defined as two or more spontaneous abortions, still remain unexplained after standard gynecological, hormonal, and karyotype investigations. However, it has been postulated that the major single cause of failed pregnancy is an error of embryo implantation, which may be as high as 78% in humans.

Embryo implantation is a complex and progressive process which involves synchronous molecular events in the uterus and the embryo promoting a perfect interaction between them. This phenomenon is characterized by apposition, adhesion and invasion of the endometrium by the blastocyst.

The establishment of consistent junctions between the embryo trophoblast and the endometrium requires the expression of adhesion molecules and elimination of nonadhesive molecules from the apical cell lining of both tissues. In this phase, called pre-implantation period, the embryo plays an important role in the receptive phase of implantation, modulating endometrial molecules and controlling the implantation process.

Prevention

3D ultrasound may inspect the cavity of the womb to ensure there is no structural abnormality preventing a pregnancy from implanting.
**Symptoms**

- implantation failure
- recurrent miscarriage

**Therapies**

**Self therapy**

Acupuncture

Acupuncture could improve the poor receptive state of endometrium due to mifepristone by promoting Th2 (T helper cell) cytokines secretion and inhibiting Th1 cytokines to improve blastocyst implantation.

**Conventional medicine**

Pharmacotherapy

Luteal support is the administration of medication, generally progestins, for the purpose of increasing the success rate of implantation and early embryogenesis, thereby complementing the function of the corpus luteum.

**Surgical therapy**

After repeated implantation failure in IVF cycles, uterine cavity should be reevaluated by hysteroscopy and this practice has been demonstrated to improve pregnancy rates.

**Assisted reproduction**

Implantation failure is the major cause negatively influencing the outcome of assisted reproductive technologies (ART), as only two out of every ten embryos successfully implant. The outcome of intracytoplasmic sperm injection (ICSI) has been shown to be positively associated with the morphological state of the sperm, while early miscarriage rates were negatively associated with nuclear morphology.
However, repeated failure of conventional IVF has been suggested to be caused by a paternal effect on early embryo development, a hypothesis confirmed using a shared oocyte donation model. Therefore, it is recommended to use special techniques of sperm selection (IMSI, PICSI, MACS etc.) to select functional sperm with undamaged DNA.

Women who have repeatedly failed in vitro fertilization (IVF) despite evidently good quality embryos can be candidates for the latest IVF therapy called endometrial scratching. Endometrial scratch-suction caused by insertion tube of (IUCD) with suction may improve the probability of pregnancy in the subsequent IVF cycle in patients who had previous failed IVF outcome by removing small polyps and any hazardous materials. The injury inflicted on the endometrium could lead to a massive secretion of growth factors and cytokines during the process of wound healing, which could help in implantation.

Find more about related issues

**Diagnoses**

**Thyroid disorders**
A medical condition impairing the function of the thyroid.
Learn more at: [www.fertilitypedia.org/therapy/diag/thyroid-disorders](http://www.fertilitypedia.org/therapy/diag/thyroid-disorders)

**Autoimmune disorders**
A condition arising from an abnormal immune response to a normal body part.
Learn more at: [www.fertilitypedia.org/therapy/diag/autoimmune-disorders-1](http://www.fertilitypedia.org/therapy/diag/autoimmune-disorders-1)

**Antiphospholipid syndrome**
A condition when immune system mistakenly attacks some of the standard proteins in blood.
Learn more at: [www.fertilitypedia.org/therapy/diag/antiphospholipid-syndrome-do-rf](http://www.fertilitypedia.org/therapy/diag/antiphospholipid-syndrome-do-rf)

**Uterine malformations**
A type of female genital malformation resulting from an abnormal development of the Müllerian duct(s) during embryogenesis.
Learn more at: [www.fertilitypedia.org/therapy/diag/uterine-malformations](http://www.fertilitypedia.org/therapy/diag/uterine-malformations)
Lupus erythematosus
Collection of autoimmune diseases in which the human immune system becomes hyperactive and attacks normal, healthy tissues.
Learn more at: www.fertilitypedia.org/therapy/diag/lupus-erythematosus

Reproductive cells

Cumulus oophorus
A group of granulosa cells that support the oocyte in an antral follicle.
Learn more at: www.fertilitypedia.org/edu/reproductive-cells/cumulus-oophorus

Embryo
A multicellular diploid eukaryote in an early stage of embryogenesis, or development.
Learn more at: www.fertilitypedia.org/edu/reproductive-cells/embryo

Endometrium
The innermost layer of uterus forming the uterine lumen where the implantation of an oocyte happens.
Learn more at: www.fertilitypedia.org/edu/reproductive-cells/endometrium

Reproductive functions

Endometrial receptivity
Period when the womb is receptive for implantation of the free-lying blastocyst.
Learn more at: www.fertilitypedia.org/edu/reproductive-functions/endometrial-receptivity

Implantation
The very early stage of pregnancy at which the embryo adheres to the wall of the uterus.
Learn more at: www.fertilitypedia.org/edu/reproductive-functions/implantation

Risk factors

Heavy metal exposure
The toxic effect of certain metals in certain forms and doses on life.
Learn more at: www.fertilitypedia.org/therapy/rf/heavy-metal-exposure
**Thrombophilia**
An abnormality of blood coagulation that increases the risk of thrombosis (formation of blood clots in blood vessels).
Learn more at: [www.fertilitypedia.org/therapy/rf/thrombophilia](http://www.fertilitypedia.org/therapy/rf/thrombophilia)

**Toxin exposure**
Toxins are small molecules, that are capable of causing disease on contact with or absorption by body tissues interacting with biologic macromolecules.
Learn more at: [www.fertilitypedia.org/therapy/rf/toxin-exposure](http://www.fertilitypedia.org/therapy/rf/toxin-exposure)

**Symptoms**

**Recurrent implantation failure**
Failure of implantation in at least three consecutive IVF attempts.
Learn more at: [www.fertilitypedia.org/edu/symptoms/recurrent-implantation-failure-1](http://www.fertilitypedia.org/edu/symptoms/recurrent-implantation-failure-1)

**Recurrent miscarriage**
A disease distinct from infertility, defined by two or more failed pregnancies.
Learn more at: [www.fertilitypedia.org/edu/symptoms/recurrent-miscarriage](http://www.fertilitypedia.org/edu/symptoms/recurrent-miscarriage)

**Therapies**

**Acupuncture**
A form of alternative medicine and a key component of traditional Chinese medicine involving thin needles inserted into the body at acupuncture points.
Learn more at: [www.fertilitypedia.org/edu/therapies/acupuncture](http://www.fertilitypedia.org/edu/therapies/acupuncture)

**Egg donation**
Process by which a woman donates eggs for purposes of assisted reproduction or biomedical research.
Learn more at: [www.fertilitypedia.org/edu/therapies/egg-donation](http://www.fertilitypedia.org/edu/therapies/egg-donation)

**Endometrial scratching**
The method during which the endometrium is gently “scratched” which causes immunological reaction leading to increase implantation rate.
Learn more at: [www.fertilitypedia.org/edu/therapies/endometrial-scratching-1](http://www.fertilitypedia.org/edu/therapies/endometrial-scratching-1)
**ERA test**
A personalized genetic test to diagnose the state of endometrial receptivity in the window of implantation.
Learn more at: [www.fertilitypedia.org/edu/therapies/era-test](http://www.fertilitypedia.org/edu/therapies/era-test)

**ICSI**
A micromanipulative fertilization technique in which a single sperm is injected directly into an egg.
Learn more at: [www.fertilitypedia.org/edu/therapies/icsi](http://www.fertilitypedia.org/edu/therapies/icsi)

**IMSI**
Method where live unstained spermatozoa are observed at 6000 or higher magnification to select sperm with the best morphology.
Learn more at: [www.fertilitypedia.org/edu/therapies/imsi-1](http://www.fertilitypedia.org/edu/therapies/imsi-1)

**Sperm donation**
The procedure in which a man (sperm donor) provides his sperm for fertility treatment.
Learn more at: [www.fertilitypedia.org/edu/therapies/sperm-donation](http://www.fertilitypedia.org/edu/therapies/sperm-donation)

**Standard IVF**
A process in which an egg is fertilised by sperm outside the body: in vitro. Own or donated gametes may be used.
Learn more at: [www.fertilitypedia.org/edu/therapies/standard-ivf](http://www.fertilitypedia.org/edu/therapies/standard-ivf)

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**Gallery**

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<th>Tab</th>
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**Criteria for defining RIF**

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of ET</th>
<th>Number of embryos</th>
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<tbody>
<tr>
<td>Coughlan, 1995</td>
<td>several</td>
<td>12</td>
</tr>
<tr>
<td>Tan, 2009</td>
<td>≥6</td>
<td>≥30</td>
</tr>
<tr>
<td>PGD Consortium</td>
<td>≥2</td>
<td>≥20</td>
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<td>Margalioth et al., 2006</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Buhimschi, 2007</td>
<td>several</td>
<td>≥8</td>
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<tr>
<td>Coughlan et al., 2014 (women under the age of 40 years)</td>
<td>≥3</td>
<td>4</td>
</tr>
</tbody>
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*Fresh or frozen ET procedures
*High-grade embryos
"An endometrial gene expression signature accurately predicts recurrent implantation failure after IVF" —by Koot et al. licensed under CC BY 4.0

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