



INDIAN FERTILITY SOCIETY

SYNAPSES

RECURRENT IMPLANTATION FAILURE (RIF)

RIF is only applicable to patients undergoing Assisted Reproductive Techniques. There is as yet no universally accepted definition for RIF and the most accepted definition is failure to achieve a clinical pregnancy after transfer of at least four good quality embryos in a minimum of 3 fresh or frozen cycles in a woman under 40 years of age.¹

Risk factors for RIF

- **Maternal Age** - As maternal age increases, aneuploidy increases because of increased chromosomal nondisjunction.² There is a decrease in mitochondrial membrane potential, increase of mitochondrial DNA damage and higher rates of embryo-endometrial asynchrony with increasing maternal age, thus leading to decreased implantation rate and live birth rate after 35 years of age.
- **BMI** - The oocyte quality and follicular development might be affected by obesity. The implantation rate decreases with increasing BMI (>25 kg/m²).
- **Smoking** - Cigarette toxins such as carbon monoxide cause depletion of oxygen to the fetus, and nicotine leads to vasoconstriction and decreased nutrients to the fetus, thus implantation may be impaired.
- **Stress** - Elevated levels of cortisol, also known as “the stress hormone,” lead to a 2.7 times greater chance (95% CI=1.2–6.2) of miscarriage within the first 3 weeks after conception in comparison to women with low cortisol levels. However, this has been refuted by studies that it is IVF failure that may lead to higher rates of both anxiety and depression in the immediate period after a negative IVF outcome.³

Pathophysiological mechanisms of Recurrent Implantation Failure.

Based on the definition proposed above, RIF is primarily due to uterine factors. However there will inevitably be a proportion of cases due to gamete or embryo factors.

- **Oocyte Factor** - The response to ovarian stimulation might be poor with fewer numbers of oocytes retrieved, a high proportion of immature oocytes, reduced fertilization rate. High FSH and low Anti-Mullerian hormone, points to poor oocyte quality. Age related aneuploidy increases as age advances. Aggressive ovarian stimulation protocols may lead to poor-quality oocytes and a higher rate of fertilization failure⁴
- **Sperm Factor** - Semen analysis doesn't reflect sperm quality. Sperm DNA damage (caused by cigarette smoking, genital tract infection and previous chemotherapy or radiotherapy)is associated with poor embryo development.⁵
- **Genetics / Parental chromosomes anomaly** - Chromosomal abnormalities like translocations, mosaicism, inversions, and deletions(translocation being most common) may lead to RIF though the overall prevalence is only about 2%.⁶ Parental karyotyping is recommended in cases of women suffering from RIF and in men with severe oligospermia.
- **Thrombophilia** - Whether hypercoagulable state leads to RIF is still debatable however prothrombotic disorders are more prevalent in RIF patients than in controls. While patients with RIF who have prothrombotic disorder might benefit from heparin treatment, for those without this abnormality empiric treatment with heparin is not justifiable.⁷ Altogether, it is recommended that patients diagnosed with RIF be investigated for acquired as well as hereditary thrombophilia disorders, and be treated accordingly.
- **Immunological Causes** - Differentiation of endometrial stromal cells (a process called decidualization), is critical for the establishment and maintenance of pregnancy. The decidualized stromal cells acquire the ability to regulate trophoblast invasion and to dampen local maternal immune responses.⁸ There is much conflicting evidence in the literature on the role of immunological factors like peripheral and uterine natural killer cells, Th1/Th2 ratio and TNF- α levels in women with RIF. There is no consensus on whether or not immunological investigations are useful and whether immunological treatment is of benefit.
- **Anatomical abnormalities and endometrial thickness** - Uterine pathologies including polyps, myomas, and adhesions can impact implantation rates in patients undergoing IVF. The anomalies can be congenital and acquired.

Anatomical Abnormalities

Congenital Uterine Pathology:

- Myomas : They can cause distortion of the endometrial cavity.
- Septate Uterus : Most common congenital anomaly . The poor outcome is related to the distortion of the uterine cavity and to the inadequate blood supply to the septum.
- Bicornuate Uterus : Women with a bicornuate uterus usually have normal implantation, but these patients have a higher risk of mid trimester pregnancy loss. These patients usually don't require surgery.

Hydrosalpinx : The fluid can negatively impact endometrial receptivity, and can also physically flush the embryo out preventing implantation.

Acquired Uterine Pathology:

Frequency of unrecognized intrauterine pathologies in patients with RIF varies between 25% and 50%.⁹

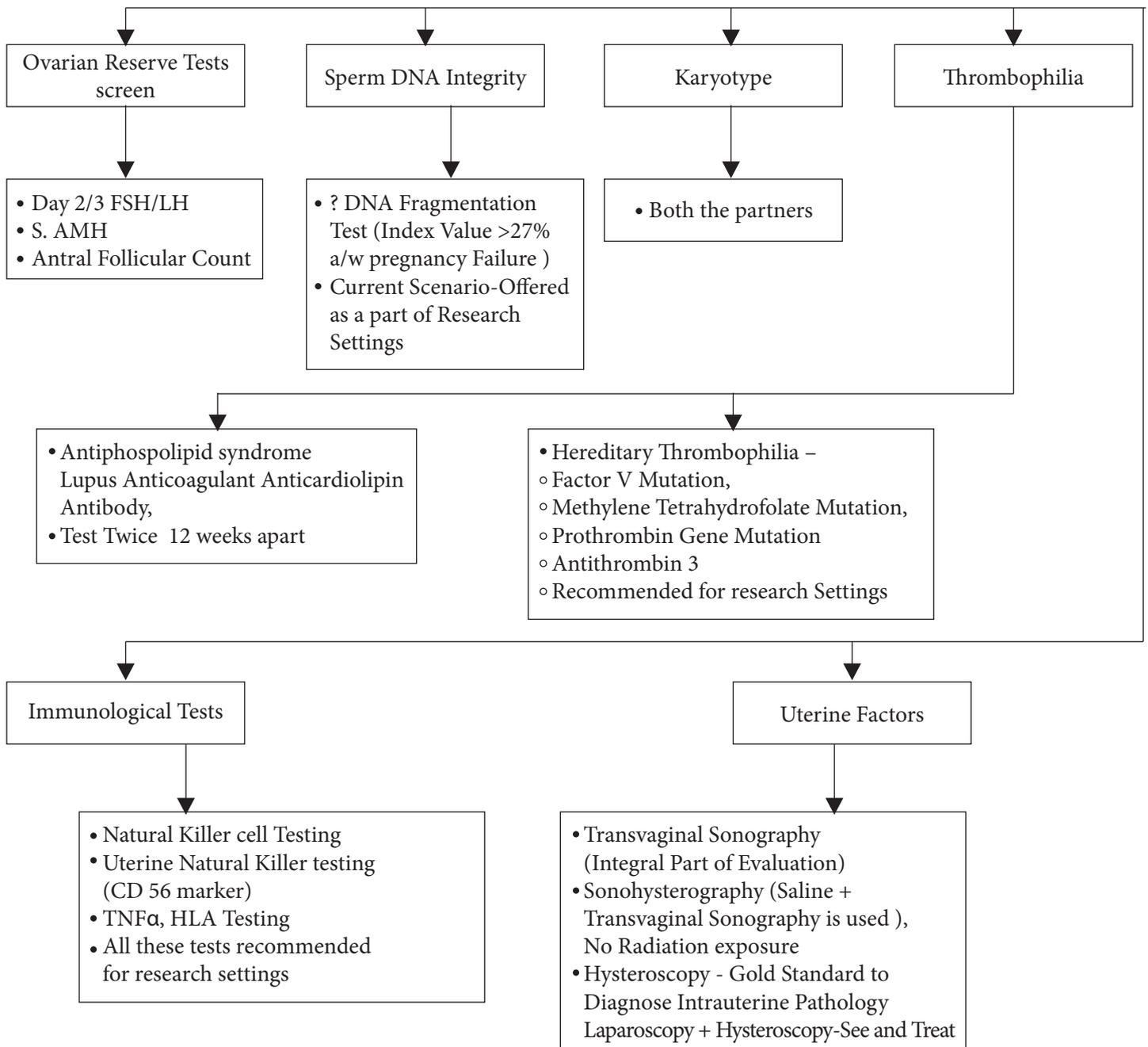
- Endometrial Polyp : Endometrial polyps may interfere with embryo implantation . The removal of endometrial polyps has been found to result in improved spontaneous pregnancy rates in various studies.
- Intrauterine adhesions : Adhesions within the uterine cavity may prevent the embryos from attaching to the luminal surface of the endometrium. Intrauterine adhesions often occur following curettage of the gravid uterus to terminate an unwanted pregnancy or in cases of retained products of conception after a pregnancy or miscarriage.

- Adenomyosis : Adenomyosis affects the junctional zone of the uterus which is just beneath the endometrium and thus implantation is affected. Unlike intramural fibroids, adenomyosis is not usually amenable to surgical treatment
- Submucous and Intramural fibroids : The submucous and intramural fibroids of >4cm may adversely affect implantation by increasing uterine contractility, deranged cytokine profile, abnormal vascularization and chronic endometrial inflammation.
- **Thin endometrium** - Thin endometrium (<7 mm) may occur following damage to the endometrium following intrauterine surgery or infection and may lead to RIF. Hysteroscopy adhesiolysis is recommended by an experienced reproductive surgeon.

Investigations

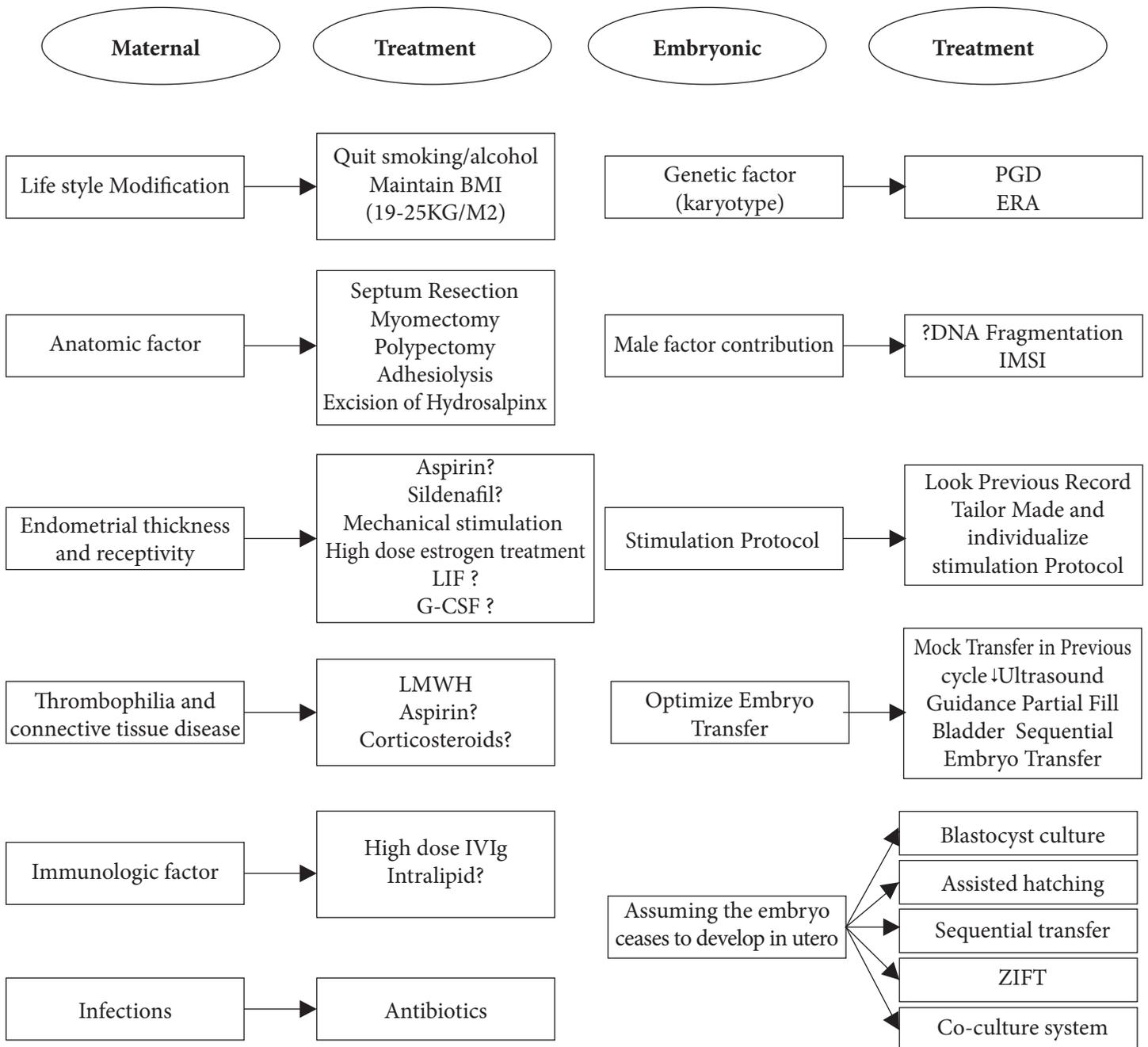
The investigations for the RIF need to be individualized after taking a detailed history and checking the previous records. Broad Outline of the investigations is mentioned in the table below.

Flow Chart for Investigations



Management

Multidisciplinary approach should be adopted in the management of a couple with RIF. Appropriate counselling and individualized treatment of the couple with RIF is of the utmost importance prior to proceeding with further treatment. A summary of the management is highlighted in the below mentioned table.¹⁰



Summary

Successful Implantation involves a synchronized cross-talk between an embryo capable of implanting, and an endometrium enabling implantation. The etiology for RIF can be attributed to the embryo itself, the mother or, in some cases, both. Women with RIF should be offered appropriate investigations to rule out an underlying cause for the repeated failure. The main treatment strategy in couples with RIF is to improve the quality of the embryos transferred and the receptivity of the endometrium.

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Dr M Gouri Devi
President

Dr Pankaj Talwar
Secretary General

Contributor

Dr Shalini Chawla Khanna
IVF Consultant

Dr Rupali
IVF Consultant
Executive Member
Chief Coordinator
Synapses - IFS

Dr Rhythm Ahuja
IVF Consultant
Co-coordinator
Synapses - IFS

+91 9667742015
+91 9899308083

☎ +91 11 40018184

✉ indianfertilitysocietydelhi@gmail.com

@ www.indianfertilitysociety.org

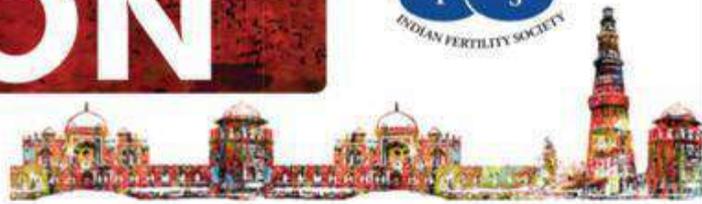
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Dr. M Gouri Devi
Organizing Chairperson
FERTIVISION 2019



Dr. Pankaj Talwar
Organizing Secretary
FERTIVISION 2019
Email-pankaj_1310@yahoo.co.in
Mob.: +91 98107 90063

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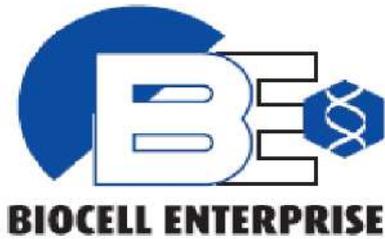
Indian Fertility Society
302, 3rd Floor, Kailash Building,
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