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RECURRENT IMPLANTATION FAILURE

Failure to achieve a pregnancy following several cycles of IVF where three good quality embryos have been transferred is defined as Recurrent Implantation Failure.

Recurrent Implantation Failure is an expected, if sad, reality of human reproduction, but it is important to recognise that not all embryos are meant to implant.

Up to 70% of embryos created, either via natural conception or IVF are lost before birth, usually within the first three months of pregnancy and most of these even before implantation.

In our experience, through persistence, investigation and taking different approaches, most patients can eventually achieve a pregnancy.

What are the causes of Recurrent Implantation Failure?

Causes of recurrent implantation failure may be varied and involve:

- the egg
- the sperm
- the embryos created
- the woman's uterus
- material & paternal health, or
- a combination of these factors

The Egg

The quality of a woman's eggs is important in creating a healthy embryo. As maternal age advances, the percentage of chromosomally abnormal eggs increases, reducing the chance of creating a healthy embryo naturally. Additionally, low ovarian reserve or a history of endometriosis and ovarian surgery, may also reduce egg health and quantity.

Investigations into egg health include:

- An AMH test which is a blood test that measures a woman's ovarian reserve (the number of eggs left in the ovary)
- Measuring the number of eggs seen on ultrasound (the antral follicle count).
- Observing the capacity of an embryo to grow to the blastocyst stage during the IVF process

There is no medical treatment that has been shown to improve the health of eggs. Approaches that have been tried, but where the evidence is still uncertain, include:

- Using antioxidants such as CoQ10 and melatonin
- Stimulating drugs to obtain more eggs
- The addition of adjuvant hormones such as low dosages of male hormone and growth hormones in patients who are defined as poor responders
- Use of pre implantation genetic testing of the embryos to identify the embryos which have normal chromosomes prior to implantation.

The Sperm

The main function of the sperm is to move and transmit healthy DNA into the oocyte to make a healthy embryo. Clearly, the fact that an embryo is forming in the first place indicates that the sperm are at least fertilising the egg. However, even beyond this point, problems in the sperm quality may still contribute to recurrent implantation failure. In some men, this may be due to advancing age or medical conditions, such as diabetes or cigarette smoking, resulting in damaged sperm DNA.

The normal first investigation for a man is a semen analysis which measures the number, movement and shapes of the sperm as well as the volume and consistency of the semen sample. This test, however, does not provide much information about the contribution of the sperm to recurrent implantation failure.

A measurement of sperm DNA fragmentation may, in some cases, provide useful information about the contribution of the sperm to the health of the embryo.

It is also important to check the male partner's chromosomes to ensure that there is no chromosomal variation underlying the problem.

What can be done to improve the health of the sperm

It is important for a prospective father to be as healthy as he can be. Problems such as excessive weight, lack of exercise, cigarette smoking or alcohol overuse can affect sperm quality as can medical conditions such as diabetes. It is an important first step for men to look after their own health and thereby improve the health of their sperm.

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There is no medical treatment that has been shown to improve the health of sperm. Approaches that have been tried, but where the evidence is still uncertain, include:

- The use of antioxidants such as zinc to improve sperm quality
- Frequent ejaculation to limit the time that sperm are exposed to endogenous free oxygen radicals that could damage the sperm DNA.
- IVF including ICSI to isolate the healthiest sperm for injection into the egg.
- We can also use a special technique using digital high magnification to select the best quality sperm
- Testicular biopsies which may yield sperm that has a lower degree of DNA damage, but the technique is invasive and still, essentially, unproven

The Embryo

One of the most common explanations for why IVF is unsuccessful, or why implantation failure or miscarriages can occur, is chromosomal variations in the embryo. These variations mean that while the embryo may start to implant, the genetic constitution of the embryo means that a viable pregnancy is either unlikely or impossible.

Chromosomal testing (preimplantation testing) of the embryo

It is possible to test the chromosomes in a human embryo prior to replacement of the embryo into the uterus. This testing ensures that embryos with a healthy chromosome constitution can be identified and replaced into the embryo. However, testing the chromosomes in an embryo does

not exclude all genetic problems in an embryo that could contribute to recurrent implantation failure.

The Uterus

Embryo implantation depends on both embryo quality and the endometrial environment. The uterus may be affected by either structural, hormonal or immunological conditions. Some of the conditions that may cause difficulties with successful implantation include

- Gynaecological disorders of the pelvis such as fibroids (muscular swellings in the uterus), polyps (small fleshy lumps in the lining of the uterus), adenomyosis (abnormal glandular tissue within the wall of the uterus)
- Scarring inside the uterus, possibly related to past uterine curettage.
- Genetic abnormalities in the shape of the uterus.
- Metabolic problems in the mother, such as mild diabetes or glucose intolerance,
- Known immune problems such as lupus or the presence of anti-cardiolipin antibodies.
- Deficiencies in the specific immune reactions in the uterus, involving the natural killer cells in the uterus that are necessary for successful implantation. This area remains complex but is a growing area of investigation.

It is also, however, important to remember that these problems are not always the cause of recurrent implantation failure. There are many conditions, such as some fibroids, which, although present, may not be affecting implantation.

Treatments for uterine problems include:

- Surgery to treat fibroids and polyps
- Laparoscopy for endometriosis

- Surgery for Intrauterine adhesions
- Medications such as clexane to assist where there are blood clotting problems.
- Immune therapies to deal with immune disorders.

General maternal and paternal health

The factors in both maternal and paternal health that could be contributing to recurrent implantation failure include:

- Body weight: a balanced lifestyle of healthy eating and exercise is recommended for patients with weight problems. For underweight patients a review by dietician is needed.
- Smoking: should be stopped
- While a low intake of coffee or alcohol does no harm, excessive alcohol and coffee intake should be reduced.
- Systemic diseases such as diabetes need to be managed adequately by the treating physician
- Blood clotting disorders and autoimmune disorders anti-phospholipid syndrome may affect miscarriage rates simple immune therapy such as heparin injections may be indicated.
- Thyroid dysfunction
- Impaired Glucose tolerance: should be treated with metformin and a suitable diet.
- Stress is, understandably, a natural part of fertility treatment. The role of stress in implantation problems remains unclear. It is, however, always a healthy approach to maintain your mental health as well as your physical health.