Recurrent IVF failure: is third party reproduction the only option?

For many couples experiencing infertility, IVF constitutes the last resort treatment, sometimes after other treatment options have also failed. Unfortunately, IVF is not always successful, and the cause for the implantation failure quite often remains unexplained. Depending on the specific circumstances, the use of donor eggs, donor sperm or even a gestational carrier are often recommended in an effort to achieve a successful outcome. These alternative treatments may not be acceptable to every couple, and many patients often need to find out why their IVF cycles have not been successful.

The reasons why some patients fail multiple IVF cycles could be very complex, and it may be difficult to find an answer despite extensive workups. In this article, I will discuss the most common reasons why embryos may not implant, the testing that can be done in an effort to find an answer, and some of the potential treatment options available for what has been called "recurrent implantation failure".

In general, the underlying cause for IVF failure can be attributed to problems with the embryos, the uterine environment, or the patient's immune system.

1. The embryos:

As women get older, the quality of their eggs declines and the resulting embryos are more likely to have chromosomal abnormalities. Embryos that don't carry a normal chromosomal component are likely to be lost soon after implantation or do not implant at all. In addition, women with diminished ovarian reserve (high FSH level on cycle day 3, abnormal Clomiphene challenge test, low inhibin B, etc.) are more likely to produce fewer eggs of lower quality, which could result in lower quality embryos.

In a small percentage of couples with recurrent implantation failure, one of the partners could have a chromosomal imbalance (i.e. chromosomal translocations) that can be screened by checking their karyotypes. In every cell of the body the genetic material is packed in structures called chromosomes that contain thousands of genes. Each cell has 46 chromosomes, including 2 sex chromosomes (the X and the Y). The karyotype is a blood test that can analyze the chromosomes in the patient's cells. For instance, an increased frequency of genetic abnormalities has been reported among men with a decreased sperm count. For those cases, PGD (preimplantation genetic diagnosis) could be offered to identify normal embryos for transfer, thereby increasing the chances of success. Even if the karyotypes from both partners are normal, couples with unexplained implantation failure have also been shown to produce a higher proportion of abnormal embryos, and a few studies have demonstrated some benefit of utilizing PGD in those patients.

A thickening of the zona pellucida (the egg shell) can occur in some patients associated with advanced age, high FSH, or recurrent implantation failure. For those patients, the embryologist in the lab can create a small opening in the egg shell utilizing a technique called assisted hatching, which may help the embryo escape and implant. Using the same technique, skilled embryologists can also remove fragments (cellular

debris between the cells) from "poor quality" embryos, improving their potential for implantation.

In some couples, the poor quality of their embryos can be also attributed to a male factor. Although the sperm contribution to embryonic development is generally more difficult to assess, a few tests are available that could help identify those cases of male factor with a low probability of achieving a successful outcome. There is some evidence that high sperm DNA fragmentation is associated with reduced fertility potential, and it can be detected with the SCSA (sperm chromatin structure assay) or the SDD (sperm decondensation assay). Unfortunately there is limited information regarding the value of these tests, and an abnormal result may not be absolutely conclusive. Since the SCSA results apparently can fluctuate from month to month, another approach is to test several samples over time, freeze them, and only use the ones with a better score for IVF. In some difficult cases however, the information obtained may help couples with severe male factor to consider utilizing donor sperm.

Treatment options for patients with poor quality embryos are limited. Often the egg quality can be improved by changing the stimulation protocol. In other cases, changing the laboratory conditions where the embryos grow can also be helpful. Coculture techniques have been developed to create a more natural environment that would enhance embryo development. The system involves growing the embryos in a culture medium over a layer of cells ("feeder" cells), instead of plastic dishes. Coculture has employed a variety of cell types for the "feeder" layer, but more recently the use of the patient's own endometrial cells from the uterine lining has been considered to be the safest choice. Although coculture techniques have been available for many years, they require several advanced techniques and experience that may not be routinely practiced in all IVF laboratories.

More advanced techniques such as cytoplasmic donation have been developed to address the problem of poor quality embryos. With this technique, a small portion of cytoplasm from a donated egg is injected into the patient's egg, prior to fertilization. Although the technique showed some early encouraging results, it has been discontinued due to safety concerns until more research is available.

Finally, for patients where the quality of the eggs is clearly the problem, egg donation may be another option available to achieve a successful pregnancy.

2. The uterus:

Evaluation of the uterine cavity to rule out fibroids, polyps or scar tissue is routine practice by most IVF programs. Uterine evaluation is usually accomplished with a hysterosalpingogram (HSG) or a saline infusion ultrasound (sonohysterography). Nevertheless, particularly for patients with good quality embryos that fail to conceive, a more thorough evaluation of the uterine cavity to rule out any uterine factors may be useful. Recent studies have shown that a hysteroscopy (visualization of the uterine cavity with a telescope) often provides significant findings in this group of patients. Likewise, an endometrial biopsy occasionally demonstrates chronic endometritis (silent inflammation of the uterine lining) in a few patients with otherwise unexplained implantation failure. Results of IVF in these cases can be dramatically improved by a simple treatment with antibiotics for two weeks. For patients with a very thin

endometrial lining, different strategies have been utilized in an effort to improve the blood supply to the uterus, including taking baby aspirin, vaginal estrogen, as well as vaginal Viagra suppositories.

The uterine environment can be negatively affected by the presence of hydrosalpinges (dilated Fallopian tubes). Women with a hydrosalpinx have lower pregnancy rates, lower embryo implantation, and a higher risk of miscarriage. The data is very clear in this regard, and removing the damaged Fallopian tubes does improve significantly the chances of success. The presence of hydrosalpinx is usually detected by HSG, laparoscopy, or even by transvaginal ultrasound if they are large enough.

A specialized endometrial biopsy occasionaly provides useful information regarding potential implantation problems. A small number of patients with unexplained implantation failure have intrinsic endometrial defects that can be detected utilizing experimental tests such as the "endometrial function test", or a test for ß-integrins.

A difficult embryo transfer can certainly result in implantation failure despite having good quality embryos due to trauma to the endometrium or difficulty in placing the embryos in the right place. With experience, most transfers can be performed smoothly, particularly with the addition of ultrasound guidance and light sedation if needed. Occasionally, patients with severely distorted anatomy can benefit from a hysteroscopy to address the problem prior to IVF.

Finally, a few patients will have uterine abnormalities that are beyond surgical repair or medical treatment. For those patients, utilizing a gestational carrier may be the only alternative that will allow them to raise their own genetic child.

3. The Immune system:

The immune system has been implicated in some cases of pregnancy failure, particularly for patients with recurrent pregnancy loss. Using the same logic, many investigators believe that a number of patients who fail to become pregnant after IVF are actually experiencing a very early loss due to immunological problems, before the pregnancy can be recognized. This topic still remains very controversial, as does the value of the different tests and the treatments advocated to treat the autoimmune disorders. At the present time, there is no agreement regarding what tests should be performed, or how to treat abnormal results. The Practice Committee Report of the American Society of Reproductive Medicine (ASRM) concluded in 1999, based on the available evidence, that antiphospholipid antibodies (APA) do not affect IVF success. They concluded that routine testing for APA is not indicated among couples undergoing IVF, and therapy is not justified. Nevertheless, a large number of immunological tests are available in an effort to identify patients with immune dysfunction, and a variety of treatments have been advocated, including baby aspirin, heparin, corticosteroids, and intravenous immunoglobulin infusions (IVIG). Due to the controversy still existing, patients should follow their physician's advice in this regard.

Even more controversial is the evaluation for inherited thrombophilias (Factor V Leiden, Protein S, Protein C, Antithrombin III, MTHFR and prothrombin G20210A mutation). Patients with those conditions have a higher risk of thrombosis (blood clotting), and pregnancy complications. Although they have been associated with

recurrent miscarriages, their impact on the outcomes of IVF has never been demonstrated.

In summary, the evaluation of the couple with recurrent implantation failure is very complex, and should be individualized for each patient. The process begins with a careful evaluation of the patient's previous history, procedures and tests that have been already performed, and a detailed review of the previous IVF cycles, including stimulation protocols, laboratory information, and embryo quality. The information will help to guide the workup in a certain direction, depending on what factors are suspected to be responsible for the lack of success. Although many tests are available, only those that will impact future treatment decisions should be obtained. Treatment recommendations should be individualized depending on the couple's expectations, as well as the anticipated realistic chances of success. With the technological advances available today, most couples should be able to find an answer to their particular problem, and together with their physician come up with a plan that will address their goals.

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