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NEW PERSPECTIVES IN THE MANAGEMENT OF RECURRENT IMPLANTATION FAILURE

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One of the most frustrating groups of patients for in vitro fertilization (IVF) specialists are those with recurrent implantation failure. The condition 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. There are two main groups of reasons for this failure: embryo factors and uterine factors. This retrospective study, performed in a private IVF center, addressed to the uterine factors, its objective being to investigate the outcome of the next IVF procedure following the management of the uterine factors in the case of couples with recurrent implantation failure. We enrolled 40 couples and used hysteroscopy as tool of management. We came to the conclusion that managing the uterine factors improved the clinical pregnancy rate for these couples.

Keywords: failure, implantation, IVF, uterine factors, hysteroscopy.

INTRODUCTION

One of the most frustrating group of patients for IVF specialists are those with recurrent implantation failure, patients who had done multiple IVF cycles, but who still do not get pregnant.

Implantation refers to the process of the embryo embedding into the endometrium to produce a pregnancy. In clinical practice implantation is considered to be successful when there is ultrasonographic evidence of intrauterine pregnancy, meaning intrauterine gestational sac. So, implantation failure means failure to reach a stage in which there is ultrasonographic evidence of intrauterine pregnancy. This may occur very early on, during the attachement or migration stages, the result being there is no objective evidence of a pregnancy (negative urine or blood pregnancy test); it may also occur later on, after the 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 was disrupted prior to the formation of an intrauterine gestational sac (biochemical pregnancy)[1].

One must be careful not to mistakenly presume that implantation failure and IVF failure are the same thing. The IVF failure may be due to cycle cancellation, poor ovarian response, fertilization failure, implantation failure or miscarriage after ultrasound confirmation of pregnancy. So the implantation failure is just a subset of IVF failure[1]. The definition of recurrent implantation failure (RIF) derived from the practice of IVF, so it changed through the years for numerous times. Its criterias are varied: from the cumulative number of transferred embryos[2, 3] and their quality[4, 5] to the number of IVF cycles[4, 6], maternal age[7, 8] and other factors. The contemporary a pproach in the definition of recurrent implantation failure is that given by Coughlan et al, 2014: failure to achieve a clinical pregnancy after transfer of at least 4 good-quality embryos in a minimum of three fresh or frozen cycles in a woman under the age of 40 years[1].

There are two main groups of reasons for RIF: embryo factors and uterine factors. Although many papers

discussed the embryo factors (such as oocyte quality, sperm quality, parental chromosomal anomalies, etc), RIF is, based on the definition proposed in 2014, most probably due to uterine factors. These can be divided into congenital uterine anomalies, like septate uterus or defects in the development or fusion of the Mullerian ducts during embryogenesis, and acquired intracavity conditions, like submucous fibroids, endometrial polyps, intrautherine adhesions and adenomyosis[1].

One of the most important investigations in women with RIF is hysteroscopy, because it allows reliable visual assessment of the cervical canal and uterine cavity. The hysteroscopy is considered to be the gold standard to diagnose intrauterine pathology and it is also a therapeutic tool for most of uterine pathology (fibroids, endometrial polyps, intrauterine adhesions, uterine septae) with minimal intraoperative and post-operative morbidity[1].

Hysteroscopy significantly increased clinical pregnancy rates in women with RIF in 2 prospective randomized controlled studies[9, 10]. For women with RIF, even if the hysterosalpingogram was normal, hysteroscopic evaluation should be offered. The incidence of unrecognized intrauterine pathologies in women with RIF was found to be between 25 and 50%[11]. If the woman with RIF had a hysteroscopy in the past prior to the commencement of infertility treatment, it should be repeated if the hysteroscopic assessment was conducted more than 2 years ago or if the patient had another intrauterine surgery since then (e.g. removal of products of conception after miscarriage).

There is evidence to suggest that submucosal and intramural fibroids that distort the endometrial cavity are associated with decreased pregnancy and implantation rates in women who attempt to conceive spontaneously or who are proceeding with IVF treatment. Several studies suggest that pregnancy rates improve following the resection of submucous fibroids, the most recent ones being one meta-analysis of existing controlled studies[12] and one randomized controlled study[13].

Talking about non-cavity-distorting intramural fibroids, some studies sugest an adverse effect on implantation and pregnancy rates in women undergoing IVF (particularly large fibroids >4 cm), whereas other studies fail to demonstrate such an association. There are three recent meta-analyses published on this particular subject[12, 14, 15]. All three analyses agree that women with intramural fibroids appear to have reduced implantation rates compared with women without intramural fibroids. However, myomectomy did not appear to significantly increase the clinical pregnancy and live birth rates[12] and the most recent meta-analysis cautioned that the available evidence is weak because of significant heterogeneity and methodological issues[14].

An endometrial polyp may also interfere with embryo implantation. A recent systematic review found that hysteroscopic removal of endometrial polyps resulted in doubling of the clinical pregnancy rate in women undergoing intrauterine insemination treatment[16]. It seems likely that endometrial polyps contribute to RIF.

Congenital uterine anomalies may affect endometrial receptivity manifesting as either infertility or recurrent pregnancy loss[17]. The septate uterus is the most common structural uterine anomaly. A recent study by Ban-Frangez et al on the outcome of singleton pregnancy after IVF/intracytoplasmic sperm injection (ICSI) showed that the presence of a septum, whether large or small, was associated with a miscarriage rate of about 80%, which was reduced to 30% or so after surgical removal of the septum[18]. There is preliminary evidence that the septate uterus may also contribute to RIF. So, in women with RIF, uterine septae should be removed, regardless of the size.

The presence of intrauterine adhesions often occurs after curettages of the gravid uterus, intrauterine surgery or intrauterine infection of the nongravid uterus and may interfere with successful implantation. Demirol and Gurgan found that intrauterine adhesions occurred in 8.5% of women with RIF[9]. The evidence available so far suggests that hysteroscopic removal of intrauterine adhesions improves fertility outcomes[19-22].

The role played by adenomyosis in reproductive failure is receiving increasing attention and is now recognized to be a cause of RIF[23]. The prevalence of adenomyosis in women with RIF is likely to be underestimated as it may not always be detected by transvaginal ultrasonography. Magnetic resonance imaging provides superior resolution and is probably the most accurate noninvasive diagnostic technique available. Adenomyosis almost always affects the junctional zone of the uterus which is just beneath the endometrium and so may have a greater impact on implantation than intramural fibroids which are some distance away from the endometrium.

Our hypothesis was that the management of the uterine factors in couples with RIF would improve the outcome of the next IVF cycle. The aim of this study was to compare the clinical pregnancy rate and the

live-birth outcome for a new IVF cycle between the women with recurrent implantation failure with and without managing the uterine factors through hysteroscopy.

MATERIAL AND METHODS

This study was a retrospective analysis of 40 fresh autologous embryo transfers performed at our center during 2014. The study was performed at Gynera Fertility Center in Bucharest. 40 patients with RIF who underwent a fresh autologous blastocyst or cleavage-stage embryo transfer (ET) cycle. Exclusion criteria were use of frozen-thaw ET and donor oocyte cycles. The patients were divided into 2 groups: one group of 20 patients with RIF for which hysteroscopy was used as a tool of management (the H group) and another group of 20 patients with RIF for which hysteroscopy was not used (the C group).

Stimulation Protocol Ovarian stimulation occurred with mixed FSH/LH protocols under GnRH-antagonist or GnRH-agonist pituitary suppression. For GnRH-antagonist cycles, the antagonist was initiated when the lead follicle was 14 mm in size. For GnRH-agonist cycles, administration of the agonist was initiated on the 21-st day of the previous cycle.

Ovarian stimulation was achieved by using recombinant FSH or human menopausal gonadotropin. When the lead follicle was ≥18 mm, final oocyte maturation was triggered with hCG, or with GnRH-agonist in some of the GnRH-antagonist cycles. Oocytes were retrieved 35-35½ hours later, and insemination was achieved with conventional IVF or intracytoplasmic sperm injection (ICSI), as clinically indicated.

Embryo transfer Ultrasound-guided ET was performed on day 3 or on day 5, if an adequate number of high-quality embryos were available. The technique used was the afterload technique, in which the outer sheath of the transfer catheter is left in place to maintain access to the uterine cavity.

Serum hCG levels were assessed 2 weeks after the trigger injection, and ultrasonographic confirmation of pregnancy was obtained in all pregnant patients.

The study was approved by the Ethical Committee, all patients signed the informed consent before being included in the study.

RESULTS AND DISCUSSIONS

Figure 1 shows that in the H group, the results of the endoscopy were as follows: 6 patients had intrauterine adhesions (which were removed), 3 patients had submucous fibroids of 0,5-1,5 cm (which were also removed), and for 11 patients the uterine cavity was found to be normal.

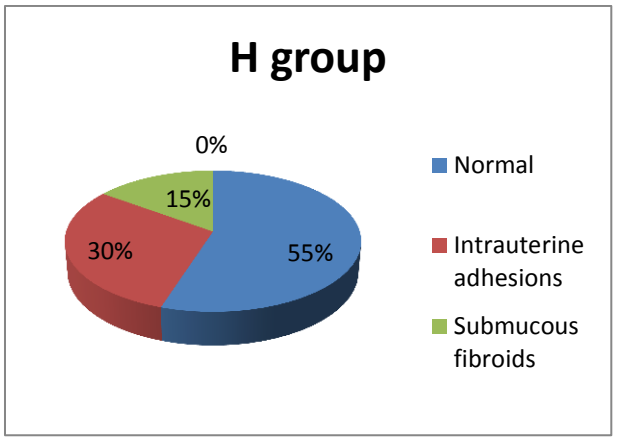

Figure 1. The results of the hysteroscopy for the H group.

The outcomes assessed were: biochemical pregnancy (detectable serum human chorionic gonadotropin), clinical pregnancy (defined as an intrauterine gestational sac on ultrasound) and live birth (defined as the birth of a live infant of ≥28 weeks of gestation).

Outcomes of the 2 groups are shown in figure 2.

Biochemical pregnancy, clinical pregnancy and live birth have a tendency to be higher in the H group than in the C group, even it cannot reach statistical significance.

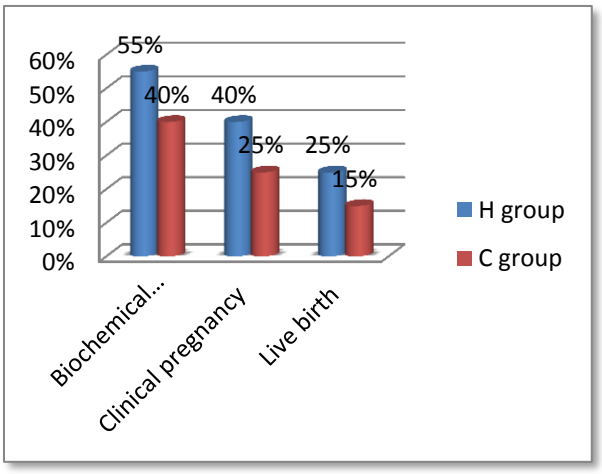

Figure 2. The outcomes for the groups C and H.

Our study showed that the presence of a submucous fibroid in women with RIF, should be removed, regardless of the size. Prior to the surgery, the size and number of fibroids and the depth of intramural extension should be carefully assessed. Resection of a solitary submucous fibroid less than 5 cm in diameter and with little intramural extension should not pose significant difficulties. However, a submucous fibroid more than 5 cm in diameter or more than 50% embedded in the intramural part of the uterus may require removal in two stages. In the case of multiple submucosal fibroids, there is an increased risk of intrauterine adhesion formation after the procedure.

Our study adds to the previous literature in accepting that intrauterine adhesions adversely affect the implantation rate and so, if present in women with RIF, should be removed. Knowing that intrauterine adhesions often recur after surgical removal and there is a high rate of complication in cases of severe intrauterine adhesions resulting in partial or complete obliteration of the cavity, their removal through hysteroscopy should be carried out by an experienced reproductive surgeon.

CONCLUSIONS

The main treatment strategy in couples with recurrent implantation failure is to improve the receptivity of the endometrium and the quality of the embryos transferred. The management of the uterine factors through hysteroscopy in couples with RIF does improve the outcome of the next IVF cycle, but further robust randomized trials are required on this topic.

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