Chapter

Recurrent Implantation Failure: The Role of Anatomical Causes

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Abstract

Recurrent implantation failure (RIF) is one of the great challenges of current reproductive medicine. The term refers to the failure of repeated transfers of embryos of good morphological quality. Embryo implantation is a crucial moment in *in vitro* fertilization (IVF) treatments. A successful pregnancy depends on a synchronized interaction between a good quality embryo and a receptive endometrium. Its failure may be a consequence of embryo quality, anatomical or immunological factors. The anatomic causes constitute an important factor for RIF, although they are usually manageable. Fibroids, polyps and adhesions that develop after a surgical procedure or infection can hamper the embryo - endometrium attachment process. In addition, Mullerian abnormalities and hydrosalpinx can cause a negative impact on implantation rates and should also be taken into account in patients with RIF. In this chapter, we will address the main anatomical causes that may impact the implantation rates of patients undergoing IVF, as well as recommendations on management and its treatment.

Keywords: implantation failure, fibroids, endometrial polyps, adhesions, uterine septum, mullerian abnormalities, hydrosalpinx

1. Introduction

Recurrent implantation failure (RIF) is one of the biggest challenges of the current reproductive medicine. Firstly, it is difficult to find its clinical standardized definition, despite the various articles on the topic. There is no agreement on issues, such as the number of embryo transfer failures, the embryo development stage, its morphology and aneuploidy, in order to define RIF [1]. There are also inconsistencies on the definition of implantation. Some authors consider it a failure when the gestational sac is not seen after the embryo transfer. Others claim that it happens when the β-hCG test is negative [1]. In 2014, some researchers proposed

the following definition: it is the transfer of at least four good morphologic quality embryos, with at least three fresh or frozen transfers to women below 40 years old. This is the most accepted definition up to date [2]. However, an international common understanding is necessary to standardize the definition in order to create more consistent scientific studies.

The embryo implantation is a key stage during *in vitro* fertilization (IVF) treatment. A successful pregnancy relies on a synchronized interaction between a good quality embryo and a receptive endometrium for implantation. Its failure can be a consequence of embryonic, anatomic or immunologic factors.

The anatomic causes constitute an important factor for RIF, although they are usually manageable. Fibroids and polyps can cause endometrial cavity distortion. Adhesions that form after surgery or infection can hinder the process of embryo implantation. Besides that, mullerian abnormalities such as septate or bicornuate uterus should be considered in patients with RIF.

According to the American Society of Reproductive Medicine (ASRM), the presence of hydrosalpinx can negatively affect implantation rates, either by alteration on the fluid nutrients or even by mechanically affecting embryo implantation.

In this chapter, we will address the main anatomic causes that can affect the implantation rates in patients undergoing to IVF as well as recommendations on the management and treatment.

2. Uterine fibroids

Submucosal fibroids can affect embryo implantation due to different mechanisms, resulting in subsequent increased uterine contractility, abnormal endometrial vascularity, chronic endometrial inflammatory response and changes in local cytokines profile.

Fibroids which distort the endometrial cavity are associated with lower implantation and pregnancy rates among women who tried a natural pregnancy as well as among those who are undergoing IVF treatment [2].

2.1 Diagnosis

Uterine fibroids investigation among women with RIF can be done through the following methods:

- Transvaginal ultrasound scan: non-invasive method performed routinely in women undergoing IVF treatment [2, 3].

- Hysteroscopy procedure: it is considered a gold standard method in the diagnosis and treatment of intrauterine pathologies which cannot be seen during a transvaginal ultrasound scan, such as for example submucosal fibroids. A guideline published recently shows that the incidence of abnormal hysteroscopic findings in women with RIF ranges from 14–51%, including the submucosal fibroids. The author mentions a large and well conducted multicenter randomized clinical trial (RCT) - the TROPHY study - which discusses the role of hysteroscopy in RIF investigation among women with normal basal transvaginal ultrasound scan results. He found uterine alterations in 24% of women in the hysteroscopy group. However, only 4% showed an incidence of surgically treated alterations. Besides that, there was no statistical difference in live births rate among the two groups after surgical correction. Therefore,

the above-mentioned guideline states that the routine hysteroscopy among RIF patients with normal basal transvaginal ultrasound scan is not recommended (recommendation strength: strong; evidence level: high) [1, 4]. Hysteroscopy must be considered before a new treatment cycle if the basal transvaginal ultrasound scan shows uterine pathology.

- Hysterosonography: although studies about cavity evaluation in RIF patients refer mainly to hysteroscopy, hysterosonography is a recommended and acceptable choice [1].

- Hysterosalpingography: it has a limited value for detection of intrauterine pathology and should not be used routinely for this purpose [2].

2.2 Treatment

Regarding the management of submucosal fibroids in women with RIF, one advocates their surgical removal, regardless the size, since evidence shows that their removal can improve clinical pregnancy rates [2, 3].

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. Some surgeons advocate the removal of the anterior wall and posterior wall fibroids on separate occasions to reduce the risk of intrauterine adhesions [2, 3].

Unlike what happens to fibroids that distort the uterine cavity, there is no consensus regarding the removal of intramural fibroids in women with RIF. Some authors suggest adverse effects of intramural fibroids on implantation and pregnancy rates in women undergoing to IVF, particularly those larger than 4 cm, while other authors could not demonstrate such association [2].

The meta-analysis papers on the topic agree that women with intramural fibroids seem to have decreased implantation rates compared to those without intramural fibroids. However, the myomectomy did not seem to significantly increase clinical pregnancy and live births rates [3]. Therefore, the pros and cons of the myomectomy must be individually assessed. The patients must be aware of the possible complications caused by the procedure such as bladder and bowel injury, hemorrhage, risk of blood transfusion and hysterectomy that occurs in 1% of cases. Other consequences would be the formation of pelvic adhesions leading to infertility due to peritoneal tube factor, and the risk of uterine rupture in subsequent pregnancies. However, one must acknowledge that intramural fibroids can cause not only implantation failure but also some obstetric complications, such as increased risk of premature delivery, premature placental abruption, intrauterine growth restriction, abnormal fetal presentation and intrapartum hemorrhage. The decision-making must be individualized, and it is strongly recommended that an experienced surgeon takes part in the definition of the treatment [2].

In RIF cases with no determinant factors, the surgical removal of large or multiples fibroids is a choice [5]. After all explanations, the decision about the procedure to be taken - expectant conduct or myomectomy – is shared with the patient.

3. Endometrial polyps

Endometrial polyps are common, affecting more than 25% of women. They can be found within all ages [6, 7], and are common among infertile women with a prevalence up to 32% [8].

The potential mechanisms in which endometrial polyps can adversely affect fertility comprise mechanical interference and the release of molecules which adversely affect the spermatozoid transportation or the embryo implantation. Evidence shows increased levels of aromatase and glycodelin, a glycoprotein which inhibits the Natural Killer (NK) cells activity, resulting in a less receptive endometrium to implantation, inflammatory markers and decreased levels of HOXA-10 and 11 messenger RNA, which are known markers for endometrial receptivity [8, 9].

3.1 Diagnosis

The investigation of polyps in women with RIF can be done through some of the following methods:

- Transvaginal ultrasound scan: An endometrial polyp normally shows as a hyperechoic endometrial mass with regular borders partially or completely occupying the uterine cavity [1]. The ultrasound scan performed in the proliferative phase of the menstrual cycle generally shows more accurate results [10].

- Hysterosonography: The addition of intrauterine contrast agent (saline solution or ultrasound gel) increases transvaginal ultrasound diagnostic accuracy [11].

- Hysteroscopy: The hysteroscopy is gold standard for the diagnosis of endometrial polyps. They can be identified by hysteroscopy in 16–26% women with unexplained infertility. Hysteroscopy can also facilitate the assessment of several endometrial polyps features, such as size, number and vascular characteristics [11].

3.2 Treatment

Endometrial polyps surgical approach is controversial. The polyp size seems not to significantly affect pregnancy rates [12, 13]. Therefore, some studies have demonstrated that the resection of recently diagnosed polyps during ovarian stimulation cycle can decrease miscarriage rates and increase clinical pregnancy and live births rates, while others do not show such benefits. Lass et al. [14] showed that polyps smaller than 20 mm emerging during IVF can be expectantly managed without compromising clinical gestation and live births rates. However, in patients with RIF there is a recommendation for polypectomy prior to embryo transfer [3].

4. Congenital uterine anomalies

Congenital uterine anomalies come from failures along any step of the mullerian duct development process during embryo development, either in the formation, fusion or reabsorption. While an arcuate uterus shows a mild form of anomaly, a bicornuate uterus represents total failure. The actual uterine malformation prevalence is difficult to be determined since many of them are asymptomatic although

they reach approximately 5.5% of the general population; 8% among infertile women and 13.5% among women with history of recurrent fetal loss [15]. A prospective observational study evaluated the prevalence of congenital uterine anomalies, including arcuate uterus, and their effect on the reproductive outcome among sub fertile women undergoing assisted reproduction. Clinical pregnancy and live births rates were similar among those with congenital uterine anomalies and the control group. There were no differences in the type of delivery, newborn gender or birthweight between the two groups. However, women with congenital uterine anomalies had more chance of premature delivery. After analysis of the anomalies subtypes, pregnancy and live birth rates were similar between arcuate and normal uterus groups. But the group with larger uterine anomalies showed worse reproductive outcomes [16].

Among the congenital uterine anomalies, the septate uterus is the most common and comprises 35% of the malformations. Its prevalence among infertile women (3%) seems to be comparable with the general population (2.3%) [15].

Women with septate uterus show increased risk of spontaneous abortion (2.9 relative risk [RR]; 95% confidence interval [95% CI] 2.0–4.1), premature delivery (2.1 RR; 95% CI 1.5–3.1) and abnormal fetal presentation (6.24 RR; 4.05–9.96 CI). They also have the lowest clinical pregnancy rates (0.86 RR; 95% CI 0.77–0.96) [17].

Little is known about the physiopathology responsible for the negative reproductive outcomes in women with septate uterus. According to a recent systematic literature review, all the eight studies which histologically investigated the septum showed that it consists of endometrial and myometrial tissue, and that most intrauterine septa are vascularized. One explanation for jeopardized reproductive outcomes of embryos implanted in the intrauterine septum could be the different histologic composition of the endometrial septum tissue. The glandular cells and the stroma have different morphologic characteristics: a smaller number of glandular cells and cilium, and incomplete cilium genesis.

Besides that, the endometrial septum contains the lowest levels of vascular endothelial growth fator (VEGF) receptors. It is believed that they have an important role in the early embryo implantation and placentation. In two studies, the HOXA10 gene expression, which is important for the early embryo implantation, seems to be altered in women with septate uterus. These findings can explain the disruptive development of the embryo implanted in the septum. However, since the studies' results on the issue are conflictive, a more detailed investigation is suggested [18].

4.1 Diagnosis

The definition of septate uterus has been discussed for a long time. Nowadays, there are three classification systems which are used worldwide. It's important to have a standardized classification system in order to prevent inappropriate or unnecessary surgical procedures and to compare reproductive results. The original classification system of the ASRM was modified and adapted. It currently uses morphometric criteria, such as the uterus internal indentation angle and internal midline cutout measurements to make a distinction between arcuated and septate uterus. It also uses the depth of uterus external surface to make a distinction between those and the bicornuate uterus. The uterus with indentation angle < 90°, length of midline internal cutout > 1.5 cm and uterine external cutout with less than 1 cm is defined as a septate uterus by the ASRM [19]. In 2012, the European Society of Human Reproduction and Embryology and the European Society for Gynecological Endoscopy (ESHRE/ESGE) published a

classification system to replace the subjective criteria of the ASRM classification system by absolute morphometric criteria. Contrary to the American classification, the arcuate uterus is not mentioned and is considered a variant from normality. Septum is defined when the internal indentation is > 50% of the uterine wall thickness and the depth of the external fissure is < 50% of the wall thickness [20]. Women with previous diagnosis of arcuate uterus made by the ASRM (around 58%) would be classified as having a septate uterus when using the ESHRE/ESGE new classification. Thus, there would be an increase on the number of surgical procedures to fix uterine anomalies, with no evidence showing that this practice is beneficial to these women [21]. Recently, a simplified classification was proposed by the Congenital Uterine Malformations Experts (CUME), where the septum is defined as the depth of the internal indentation ≥ 10 mm [22]. It demonstrates the heterogeneity in the classification of mullerian malformations, making it difficult to produce scientific papers on these alterations in a homogeneous way.

4.2 Treatment

The uterine septum is the only malformation that can be corrected. There are many discussions about the impact of the septum resection on the reproductive results and if it improves natural conception rates and implantation rates after embryo transfer. Nowadays, the ASRM guidelines for septate uterus management recommend the hysteroscopic resection [18]. In contrast, the ESHRE, the National Institute for Health and Care Excellence (NICE) and the Royal College of Obstetricians and Gynecologists (RCOG) guidelines for recurrent fetal loss associated to septate uterus do not support this procedure until further studies can demonstrate its effectiveness [23–25]. Lavergne et al. found a retrospective multicentric study which shows that implantation rates after IVF cycle were significantly lower in patients with malformed uterus (septate, bicornuate or unicornuate) in comparison with patients with a normal uterus (6% vs. 12%, $p < 0.01$). There was significant improvement when the uterine anomaly was corrected (septate uterus) [26]. One study compared gestation and abortion rates after embryo transfer on an IVF cycle in patients with septate uterus before and after septum resection. They were compared to a control group, showing that pregnancy rates before hysteroscopic resection (both in women with septate or subseptate and arcuate uterus) were significantly lower in comparison to the patients in the normal control group [OR 2.9 ($P < 0.002$) and 2.2 ($P < 0.001$)], respectively. After surgery, pregnancy rate was comparable to the women with a normal uterus (OR 1.2 and 1.1). The uterine septum size did not influence pregnancy rate. The study conclusion recommends the hysteroscopic resection in order to improve the reproductive outcome, not limited to women with recurrent early fetal loss or premature labor, but it is also recommended to infertile women in order to improve pregnancy and live birth rates, especially if IVF is a choice [27]. Ozgur et al. showed that a history of abortion and IVF failure was frequent among women with untreated incomplete septate uterus in comparison to the infertile general population. After surgical correction of the septum, pregnancy rates in IVF cycle were similar to the group with normal uterine cavity [28]. In a recent article by the SWOT infertility group in Spain, the researchers stated that a septate uterus has been associated to a high prevalence of repeated implantation failure in assisted reproduction and abortion after IVF. In these cases, septum resection seems to be useful to improve IVF pregnancy rates [29]. These studies suggest that the correction of anatomical alterations which distort the uterine cavity, especially the septate uterus, can improve reproductive results.

In other studies, we saw that the septate uterus correction may not bring benefits. In an international multicentric cohort study with women with septate uterus and showing desire for pregnancy (which opted for septum resection or expectant approach), Rikken et al. showed that the septum resection did not increase the chance of live births nor reduced the risk of abortion or premature birth [30]. The only controlled randomized trial assessing the reproductive outcome after uterine septum resection was recently published. Women in reproductive age with a septate uterus and the wish to get pregnant and a history of subfertility, fetal loss or premature birth were selected. The results of this randomized clinical trial showed that the hysteroscopic resection of the septum did not improve live birth rates or other reproductive outcomes in women with septate uterus. In this study, one patient undergoing septum resection had a perioperative uterine perforation. The authors concluded that if there is no proven efficacy, they do not recommend septum resection as a routine procedure in clinical practice. Women with septate uterus need to be informed about this study data. After counseling and according to the principles of shared decision-making, an informed consent must be provided [31].

In relation to other malformations, except septate uterus, surgical correction seems not to bring benefits. Surrey et al. demonstrated that the arcuate uterus does not have an impact on the results of IVF cycle after euploid embryos transfer. Women undergoing IVF with indentation between 4 and 10 mm experience excellent results which are similar to those of women with internal indentation < 4 mm (live birth rate; 68.7% vs. 68.7%). Besides that, there were no differences in the reproductive outcome among those with arcuate or normal uterus, according to Salim et al. Criteria [32]. Chen et al. compared the reproductive outcome between unicornuate and morphologically normal uterus. There were no significant differences in the pregnancy, clinical pregnancy or live births rates. The abortion rates were similar. In single pregnancies, there were no differences in the preterm birth, birthweight or birth size rates. However, prematurity rates, lower birthweight and lower birth size rates as well as higher very low birth rates were found in twin pregnancies with unicornuate uterus. A single embryo transfer is recommended for unicornuate uterus [33].

The difficulty of having an agreement on the scientific studies is due to the impediments to unite mullerian malformations classification, differences on the definition of recurrent embryo implantation failure and a low prevalence of these events. Thus, we suggest the individualization of the cases in which mullerian malformations and recurrent implantation failure appear. Among all the malformations, the septate uterus is the one whose correction is possible in order to improve the reproductive outcome. Nevertheless, further studies are necessary to confirm this statement.

5. Intrauterine synechiae

Intrauterine synechiae, intrauterine adhesions or Asherman syndrome are names that define lesions on the endometrial tissue caused after aggressive curettage or any other intrauterine procedure that destroys the endometrium.

It is known that gestational complications such as missed or incomplete abortion and afterbirth bleeding are responsible for approximately 90% of the cases [34]. Nonetheless, infections in a non-pregnant uterus and surgeries such as myomectomies or septoplasty, for example, can lead to synechiae formation [35], causing or not secondary amenorrhea.

In terms of physiopathology, the assessment by electronic microscopy shows that the glandular cells have severe alterations in women with Asherman syndrome.

It is mainly due to ribosome metabolism which culminates in ATP depletion and subsequent tissue hypoxia. There is an abnormal expression of different growth factors which leads to the activation of cytokines related to the adhesion and a pro-inflammatory cascade [36]. There are also theories that associate the occurrence, severity and recurrence of intrauterine adhesions to an alteration of the endometrial microbiome, but they lack strong scientific evidence.

The presence of adhesions in the uterine walls can interfere in the embryo implantation impeding the embryo cellular fixation on the endometrial luminal layer. Demirol and Gurgaon found a prevalence of 8.5% of intrauterine synechiae in women with embryo implantation failure, which confirms the importance of a clinical investigation [37].

5.1 Diagnosis

For 20 years, the hysterosalpingography was the first line exam for the diagnosis of intrauterine synechiae. Today it is still used by many gynecologists for the evaluation of the uterine cavity, since it is a low-cost analysis showing 75% sensitivity [38]. It is similar to the hysterosonography whose sensitivity is of 82% [39]. The transvaginal ultrasound scan is also used to confirm a thin endometrium, but it has low accuracy for the diagnosis of synechiae [40], so that it is not considered the best method of investigation. The 3D hysterosonography has 91.1% sensitivity and 98.8% specificity, which makes it a good examination for the diagnosis of intrauterine adhesions [41]. However, despite the data forementioned, the hysteroscopy is certainly a golden standard for the diagnosis of synechiae, once it allows direct visualization of the uterine cavity [42] and enables treatment. There is concrete evidence that the synechiae lysis during hysteroscopy improves the reproductive outcomes [43].

5.2 Treatment

Before hysteroscopy, cervix dilation and curettage associated with estrogenic therapy and use of IUD ensured 84% success rate in the treatment of Asherman syndrome. However, today we have the hysteroscopy as a golden standard in the diagnosis and treatment of this endometrial complication. It became necessary to define the site and severity of intrauterine adhesions. Classifying the disease process can be important once the severity imposes the prognosis after treatment [44]. The hysteroscopy enables the amplification and general observation of adhesions allowing the viewing of all structures, which decreases the risk of uterine perforation. However, there should be maximum care when using mechanic and electronic section since errors can bring undesirable repercussions [45].

The surgical treatment shows success rate after adhesiolysis ranging between 75 to 100% [46]. This rate can be evaluated by the return of menstrual periods, rates and pregnancy outcome. After a hysteroscopic surgery, around 92 to 96% of women returned to their bleeding pattern prior to the syndrome showing 63% pregnancy rate and 75% live births rate [44]. The most frequent complication in pregnancies after hysteroscopic treatment for uterine adhesions is the abnormal placentation [44].

The intraoperative fluoroscopy and transabdominal ultrasound scan or the laparoscopy are also efficient alternatives [45]. The fluoroscopic guidance enables the surgeon to see endometrium islands behind the scar tissue in an obliterated uterine cavity. The radio opaque dye is injected into a dense scar area in the place where the cavity is obliterated. Some endometrial adhesions can be identified using fluoroscopy. The area can be opened through acute dissection under hysteroscopy.

However, this technique is considered limited by the high cost, by technical difficulties or by the requirement for ionizing radiation [46].

The laparoscopic guidance for severe cases of intrauterine adhesiolysis has been advocated for the immediate recognition and treatment of uterine perforation, thus minimizing the extrauterine trauma. The intraoperative ultrasound scan, fluoroscopy or laparoscopy together with the hysteroscopy have been used as guidance to reduce the risk of perforation. Nevertheless, nowadays it is known that these interventions do not prevent uterine perforation or improve the outcome [46].

The stem cell therapy approach is much more efficient due to the potential for multiplication of a single cell and its transformation into undifferentiated forms (self-renovation) and into mature cells. Besides that, it can produce other types of cells, such as totipotent, pluripotent and multipotent cells [35].

In 2016, Tan et al. [47] investigated mesenchymal stem cells derived from bone marrow and stromal cells coming from the menstrual bleeding through transmiometral administration in the subendothelial area, direct installation of stromal cells in the uterine cavity and infusion of cells in spiral arteries through a catheter. Five out of six women with Asherman syndrome recovered their menstrual periods. Others reached adequate endometrial thickness and regular menstruation cycles and were able to get pregnant right after that. In this study, the authors compared some types of stem cells and could observe endometrial regeneration in most of the cases.

Thus, stem cells therapy has become a new method of treatment for the regenerative medicine, and more specifically, for the regeneration of endometrial diseases with Asherman syndrome and thin endometrium. However, stem cells transplant for Asherman syndrome is far from being common [46].

The biggest challenge for the treatment of Asherman syndrome is to prevent the recurrence of adhesions after the early treatment, which reaches 66% [46]. The treatment is defined by time. There are studies that evaluated the post-operative period comparing the use of intrauterine device (IUD) with intrauterine balloon catheter, Foley catheter, hormonal treatment and barriers such as amniotic membranes. The results are conflicting.

For instance, the copper IUD can provoke inflammation and is contraindicated [44]. Similarly, the hormone IUD have a small surface that limits its capacity to keep the endometrial cavity walls separated during healing [39]. The risk of infection after the insertion of an IUD after surgical resection of intrauterine adhesions is about 8% [44].

The placement of a Foley catheter with an IUD was assessed as a possible adjuvant treatment to prevent the formation of synechiae after hysteroscopy. The authors concluded that the Foley catheter placed one week and a half after adhesiolysis showed 81% success rate while the group which placed an IUD twelve weeks after the adhesiolysis showed 62% success rate [48]. The use of intrauterine hyaluronic gel after hysteroscopic treatment reduces adhesions recurrence [48], but further studies are needed for its incorporation into the treatment [44, 45].

Platelet-rich plasma (PRP) is a form of treatment for intrauterine adhesions after operative hysteroscopy and may be a substitute for the intrauterine balloon. However, randomized controlled trials with large sample sizes are warranted to further confirm the conclusions to compare the efficacy of intrauterine infusions of PRP with intrauterine balloons applied immediately after transcervical resection of the adhesions by hysteroscopy [49].

Clinical treatment with drugs such as aspirin, sildenafil and nitroglycerin have been done to increase endometrial blood flow in an attempt of stimulate cell regeneration. Successful pregnancies were reported after using them. However, more robust and well designed studies are required to confirm it [44].

Hormonal therapy with post-operative estrogen was not standardized in terms of dose, duration, route of administration or a combination with progesterone, Data about its efficacy are limited [44]. The American Association of Gynecologic Laparoscopists (AAGL) guidelines recommend hormonal therapy with estrogen after adhesiolysis, but there is no definition for dose or standard regimen [46]. The combination of this and adjuvant treatments is necessary for a maximum effect on patients with mild to severe adhesions.

As for the therapy with antibiotics, there is a lack of studies addressing the risks and benefits of those before, during and after surgical lysis of intrauterine adhesions. The American College of Obstetrics and Gynecology (ACOG) does not recommend the routine use of antibiotics with this objective [44, 46].

Hysteroscopic adhesiolysis cure infertility in mild, moderate and severe IUA in around 90, 70 and 30%, respectively [50]. Gestational surrogacy remains an alternative for those patients with intrauterine adhesions that stay infertile [51].

6. Adenomyosis

Adenomyosis is a benign uterine pathology known by the invasion of glandular endometrial tissue and myometrial stromal tissue which leads to disorders in the myometrial natural architecture [52].

There are some theories explaining the emergence of adenomyosis. The theory of tissue injury and repair (TIAR) as the main mechanism of myometrial invasion has been the most accepted hypothesis. Chronic peristaltic myometrial contractions can lead to micro lesions close to the endometrial-myometrial junction causing inflammation which in turn leads to an increase in local production of estrogen inducing a vicious cycle. Thus, the TIAR theory highlights the importance of tissue damages to the endometrial-myometrial interface supporting the common knowledge that the adenomyosis is associated with multiple births, previous cesarean section and previous uterine surgery [53]. However, it is known that there is a considerable number of macrophages in the ectopic endometrium of patients with endometriosis, fibroids and adenomyosis. Therefore, the potential for embryo implantation can be affected by adenomyosis [54]. This increase in the number of macrophages induced by adenomyosis can cause a hostile immunologic environment for embryos transferred during the implantation process. The interleukin-1 alpha tumor necrosis factor as well as reactive oxygen and nitrogen species are potentially toxic for embryos. It was demonstrated that an increased level of nitric oxygen is related to an adverse development of embryos and low pregnancy rates in the endometrial environment in patients with adenomyosis. Besides that, endometrial biopsies taken from adenomyosis showed that this tissue is composed of a high quantity of antioxidant enzymes as superoxide dismutase, catalase and glutathione peroxidase which are clear signs of oxidative stress caused by excessive ROS production [55].

Other risk factors are age over 40 years, multiple births, previous cesarean sections or other uterine surgeries. The disease is often diagnosed in young and infertile women or those with pain or abnormal uterine bleeding, or both [56].

Adenomyosis is associated with a great variety of symptoms. The common symptoms include pelvic pain (as dysmenorrhea, dyspareunia or chronic pelvic pain), abnormal uterine bleeding and impaired reproductive potential or even infertility itself. However, it is important to observe that 30% of women with adenomyosis have no symptoms [57]. In infertile women with adenomyosis, the topic endometrium shows a great variety of molecular alterations causing altered receptivity. That includes the alteration in the sexual steroid hormone via, increase

of inflammatory markers and oxidative stress, decrease on the implantation markers expression, lack of adhesion molecular expression and altered gene function for the embryo development. Not only fertility outcomes are affected, but also pregnancy outcomes [58]. These include premature birth, premature rupture of membranes, postpartum hemorrhage, abnormal fetal presentation, increase on the risk of abortion in the second trimester and abnormal placental position [57].

6.1 Diagnosis

The diagnosis can be done after case history, clinical evaluation and image assessment with 2D/3D transvaginal ultrasound or magnetic resonance [52]. The transvaginal ultrasound for its facility of access and low cost in relation to other types of screenings has become a very useful tool to the diagnosis. Several ultrasographic criteria have been used to the adenomyosis diagnosis, including uterine size increase, anterior and posterior uterine walls thickness asymmetry, presence of heterogeneous myometrial areas, presence of myometrial anechoic areas, presence of sub endometrial echogenic striations, sub endometrial echogenic nodules, irregular endometrial-myometrial interface, poor definition and thickness of the junctional zone [57].

A meta-analysis about ultrasound accuracy in the diagnosis of adenomyosis demonstrated 82.5% sensitivity (95% CI), 77.5–87.9) and 84.6% specificity (95% CI, 79.8–89.8) with 4.7 positive likelihood ratio (3.1–7.0) and 0.26 negative likelihood ratio (0.18–0.39) which is comparable to the magnetic resonance [59].

The magnetic resonance is a precise and non-invasive technique used to the diagnostic of adenomyosis [60]. Its sensitivity and specificity in this diagnostic range from 88–93% and 67–91%, respectively [57]. The diagnosis of adenomyosis by magnetic resonance is essentially related to junctional zone characteristics, but can also include direct and indirect signs of endometrial glands inside the myometrium and smooth muscle cells hypertrophy [61, 62].

6.2 Treatment

Clinical pregnancy, implantation, and ongoing pregnancy rates were significantly higher in women undergoing frozen embryo transfer after long-term GnRH-analog therapy compared to those not pretreated with GnRH-analog [63].

Tremellen et al. reported that hypothalamic–pituitary- ovarian axis suppression therapy with GnRH agonist can produce a significant decrease in the number of endometrial macrophages, presumably interfering with the estradiol-mediated recruitment of macrophages to the endometrium and a subsequent normalization of embryo implantation rates [64]. Wang et al. showed that patients with normal ovarian reserve who underwent IVF/ICSI, adenomyosis seemed to negatively affect IVF/ICSI outcomes after a long GnRH agonist protocol (subcutaneous administration of short acting GnRH agonist on the dosage of 0.1 mg/day, for 10 days followed by 0.05 mg/day until the day of hCG injection which was started in the mid-luteal phase of the previous cycle), but patients with adenomyosis following an ultra-long GnRH-agonist protocol could experience stronger pituitary inhibition and lower ovarian responses but still could have a better IVF/ICSI outcomes. Ultra-long GnRH agonist protocol was considered the use of a depot injection of the long-acting GnRH agonist, triptorelin acetate (triptorelin) 3.75 mg, intramuscularly, every 28 days for at least 3 months before starting ovarian stimulation [65]. This therapy may produce a window of time with improved implantation rates [66].

The use of a levonorgestrel-releasing intrauterine device, danazol, or aromatase inhibitors may temporarily induce regression of adenomyosis and oral contraceptive

pills, high-dose progestins, and selective progesterone receptor modulators can temporarily improve its symptoms, but these are not used in fertility treatments [66].

Patients with adenomyosis present a higher number of uterine contractions. Oxytocin (OT), a nonapeptide synthesized by neurons of the supraoptic nucleus and released from the posterior pituitary gland, has diverse effects on the female reproductive system. It is known to be a factor causing uterine contractions. It has also been shown in animal models that endometrial cells contain oxytocin receptors (OTRs) and that OT has the capacity to trigger the production of prostaglandin (PG) F2a from these cells. Atosiban, an OTR antagonist, treatment before ET in endometriosis is effective in the priming of the uterus, suitable for embryo implantation [67]. Since uterine contractions in IVF cycles are significantly increased following ovarian stimulation and women with frequent uterine contractions have a lower pregnancy rate, the use of atosiban around embryo transfer may resulted in higher pregnancy rates in women with RIF and adenomyosis. According to Hung Yu et al., the use of atosiban around embryo transfer did not improve the live birth rate in a general population of IVF patients [68].

7. Hydrosalpinx

Hydrosalpinx refers to a condition in which the fallopian tube is filled with fluids following infundibulum obstruction. It is a common condition among infertile women with 10–13% diagnosis rate after ultrasound scan. These numbers can be increased when other diagnostic methods such as hysterosalpingography or laparoscopy are used [69].

Perhaps the real cause for the implantation failure is not known, but studies suggest a decrease in live births rates in patients with hydrosalpinx [70].

The theories regarding hydrosalpinx and implantation failure are about a possible embryo toxicity, changes in the endometrium quality or even embryos washout mechanical effect [71].

The endometrial involvement secondary to hydrosalpinx is related to the presence of fluid inside the uterine cavity, altered endometrial flow, altered in inhibiting factors and increase in the inflammatory response. Besides the endometrial changes and a possible embryo toxicity, the implantation failure can be related to a negative effect on sperm motility and survival.

7.1 Diagnosis

A history of ectopic pregnancy, pelvic inflammatory disease, endometriosis or previous pelvic surgery increase the suspect of infertility by tubal factors [72]. For patients without risk factors, a negative antibody test for chlamydia indicates that there is less than 15% chance of tubal pathologies [73]. For an accurate diagnosis and an effective treatment of the tubal blockage it is necessary to do exams as the hysterosalpingography (HSG) which uses water or lipids soluble contrast medium. It is a golden standard method to evaluate tubal permeability and can bring some therapeutic benefits. The HSG can document tubal blockage in proximal and distal sites, show salpingitis isthmic nodosa, reveal fimbrial phimosis or peri tubal adhesions [74]. The HSG positive and negative predictive factors are 38% and 94%, respectively [75].

The laparoscopy with chromotubation with methylene blue test (dye test) injected thorough the cervix can demonstrate tubal permeability, proximal or distal tubal occlusion. This surgical route can also identify and correct peritoneal and tubal factors such as fimbriae or peri tubal adhesions which cannot be seen with less invasive methods as the HSG [74].

7.2 Treatment

The techniques used for the treatment of hydrosalpinx are many: laparoscopy or laparotomy for salpingectomy, salpingostomy or even uterine proximal occlusion.

A meta-analysis published in 2020 evaluated the effect of hydrosalpinx on the pregnancy rates, compared different types of treatment and the impact on the ovarian reserve after treatment for hydrosalpinx [70]. They reviewed 17 studies and observed that the hydrosalpinx was associated with a significant decrease in the implantation rate with embryo transfer with 0.41 OR [0.32–0.53]. Besides that, the clinical pregnancy rate per subject and per transference significantly decreased in women with hydrosalpinx (OR = 0.54; [0.32–0.89] and 0.44 [0.27–0.73], respectively) [70].

The hydrosalpinx removal with salpingectomy leads to an improvement of in vitro fertilization outcomes in comparison with no treatment, which turns it into a golden standard management before IVF. This evidence is replicated in other studies, such as Palagiano et al., where the pregnancy rates in patients with hydrosalpinx is lower than the control group [69]. There were negative effects either in fresh or frozen embryo transfers. An increase of two or threefold in abortions in women with hydrosalpinx was observed.

The hydrosalpinx mechanism action is still uncertain. Studies show a negative impact in IVF treatment outcomes, including a decrease in implantation rates, clinical pregnancy and in course pregnancies. Besides that, they show a risk of miscarriages (1.68 OR) and ectopic pregnancy (3.48 OR), according to Capmas et al. [70]. The salpingectomy is the treatment that increases success rate and prevents secondary aggressive factors. According to some authors, it is considered a golden standard. But it can be related to a decrease in the Anti-Mullerian Hormone average of 0.99 ng/ml, as shown the meta-analysis by Capmas et al. [70].

8. Conclusion

The recurrent implantation failure is a complex clinical condition with a wide variety of etiologies. Its criteria are not still well defined. Despite the lack of consensus, studies strongly show that anatomical factors affecting the uterine cavity contribute to implantation failure. Most of these factors are treatable, though.

Each patient approach must be individualized and offered to women with adequate RIF investigations to eliminate the possibility of all structural causes. The lack of success of an IVF can be devastating for some couples.

Uterine pathologies such as fibroids, adenomyosis, endometrial polyp, congenital abnormalities and synechiae must be considered in the diagnosis of RIF and must be excluded using image exams. Hydrosalpinx is known as a factor for implantation failure and a laparoscopy with salpingectomy or uterine proximal occlusion must be offered as a therapy option.

Even after more than 40 years of IVF procedures worldwide, the causes of RIF remain challenging and controversial. It is necessary to establish a consensus about diagnosis and therapeutic approaches to reduce expensive treatments which are not efficient and are time-consuming for infertile patients.

Conflict of interest

"The authors declare no conflict of interest."

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References

[1] Shaulov T, Sierra S, Sylvestre C. Recurrent implantation failure in IVF: A Canadian Fertility and Andrology Society Clinical Practice Guideline. Reprod Biomed Online. 2020 Nov;41(5):819-833. DOI: 10.1016/j.rbmo.2020.08.007.

[2] Coughlan C, Ledger W, Wang Q, Liu F, Demirol A, Gurgan, Cutting R, Ong K, Sallam H, Li T.C. Recurrent implantation failure: Definition and management. *Reprod. Biomed. Online.* 2014; 28: 14-38. DOI: 10.1016/j.rbmo.2013.08.011.

[3] Coughlan C. What to do when good-quality embryos repeatedly fail to implant. Best Pract Res Clin Obstet Gynaecol. 2018 Nov;53:48-59. DOI: 10.1016/j.bpobgyn.2018.07.004.

[4] El-Toukhy T, Campo R, Khalaf Y, Tabanelli C, Gianaroli L, Gordts SS, Gordts S, Mestdagh G, Mardesic T, Voboril J, Marchino GL, Benedetto C, Al-Shawaf T, Sabatini L, Seed PT, Gergolet M, Grimbizis G, Harb H, Coomarasamy A. Hysteroscopy in recurrent in-vitro fertilisation failure (TROPHY): a multicentre, randomised controlled trial. Lancet. 2016 Jun 25;387(10038):2614-2621. DOI: 10.1016/S0140-6736(16)00258-0.

[5] Penzias AS. Recurrent IVF failure: other factors. Fertil Steril. 2012 May;97(5):1033-8. Erratum in: Fertil Steril. 2013 Jan;99(1):297. DOI: 10.1016/j.fertnstert.2012.03.017.

[6] Antunes A Jr, Costa-Paiva L, Arthuso M, Costa JV, Pinto-Neto AM. Endometrial polyps in pre- and postmenopausal women: factors associated with malignancy. Maturitas. 2007 Aug 20;57(4):415-21. DOI: 10.1016/j.maturitas.2007.04.010.

[7] Nijkang NP, Anderson L, Markham R, Manconi F. Endometrial polyps: Pathogenesis, sequelae and treatment. SAGE Open Med. 2019 May 2;7:2050312119848247. DOI: 10.1177/2050312119848247.

[8] Munro MG. Uterine polyps, adenomyosis, leiomyomas, and endometrial receptivity. Fertil Steril. 2019 Apr;111(4):629-640. DOI: 10.1016/j.fertnstert.2019.02.008.

[9] Richlin SS, Ramachandran S, Shanti A, Murphy AA, Parthasarathy S. Glycodelin levels in uterine flushings and in plasma of patients with leiomyomas and polyps: implications for implantation. Hum Reprod. 2002 Oct;17(10):2742-7. DOI: 10.1093/humrep/17.10.2742.

[10] Nalaboff KM, Pellerito JS, Ben-Levi E. Imaging the endometrium: disease and normal variants. Radiographics. 2001 Nov-Dec;21(6):1409-24. DOI: 10.1148/radiographics.21.6.g01nv211409.

[11] American Association of Gynecologic Laparoscopists. AAGL practice report: practice guidelines for the diagnosis and management of endometrial polyps. J Minim Invasive Gynecol. 2012 Jan-Feb;19(1):3-10. DOI: 10.1016/j.jmig.2011.09.003.

[12] Bozdag G, Aksan G, Esinler I, Yarali H. What is the role of office hysteroscopy in women with failed IVF cycles? Reprod Biomed Online. 2008 Sep;17(3):410-5. doi: 10.1016/s1472-6483(10)60226-x. PMID: 18765013. Bozdag G, Aksan G, Esinler I, Yarali H. What is the role of office hysteroscopy in women with failed IVF cycles? Reprod Biomed Online. 2008 Sep;17(3):410-5. DOI: 10.1016/s1472-6483(10)60226-x.

[13] Pérez-Medina T, Bajo-Arenas J, Salazar F, Redondo T, Sanfrutos L, Alvarez P, Engels V. Endometrial polyps

and their implication in the pregnancy rates of patients undergoing intrauterine insemination: a prospective, randomized study. Hum Reprod. 2005 Jun;20(6):1632-5. DOI: 10.1093/humrep/deh822.

[14] Lass A, Williams G, Abusheikha N, Brinsden P. The effect of endometrial polyps on outcomes of in vitro fertilization (IVF) cycles. J Assist Reprod Genet. 1999 Sep;16(8):410-5. DOI: 10.1023/a:1020513423948.

[15] Corroenne R, Legendre G, May-Panloup P, El Hachem H, Dreux C, Jeanneteau P, Boucret L, Ferré-L'Hotellier V, Descamps P, Bouet PE. Surgical treatment of septate uterus in cases of primary infertility and before assisted reproductive technologies. J Gynecol Obstet Hum Reprod. 2018 Nov;47(9):413-418. DOI: 10.1016/j.jogoh.2018.08.005.

[16] Prior M, Richardson A, Asif S, Polanski L, Parris-Larkin M, Chandler J, Fogg L, Jassal P, Thornton JG, Raine-Fenning NJ. Outcome of assisted reproduction in women with congenital uterine anomalies: a prospective observational study. Ultrasound Obstet Gynecol. 2018 Jan;51(1):110-117. DOI: 10.1002/uog.18935.

[17] Chan YY, Jayaprakasan K, Tan A, Thornton JG, Coomarasamy A, Raine-Fenning NJ. Reproductive outcomes in women with congenital uterine anomalies: a systematic review. Ultrasound Obstet Gynecol. 2011 Oct;38(4):371-82. DOI: 10.1002/uog.10056.

[18] Rikken J, Leeuwis-Fedorovich NE, Letteboer S, Emanuel MH, Limpens J, van der Veen F, Goddijn M, van Wely M. The pathophysiology of the septate uterus: a systematic review. BJOG. 2019 Sep;126(10):1192-1199. DOI: 10.1111/1471-0528.15798.

[19] Practice Committee of the American Society for Reproductive Medicine. Electronic address: ASRM@asrm.org; Practice Committee of the American Society for Reproductive Medicine. Uterine septum: a guideline. Fertil Steril. 2016 Sep 1;106(3):530-40. DOI: 10.1016/j.fertnstert.2016.05.014.

[20] Di Spiezio Sardo A, Campo R, Gordts S, Spinelli M, Cosimato C, Tanos V, Brucker S, Li TC, Gergolet M, De Angelis C, Gianaroli L, Grimbizis G. The comprehensiveness of the ESHRE/ESGE classification of female genital tract congenital anomalies: a systematic review of cases not classified by the AFS system. Hum Reprod. 2015 May;30(5):1046-58. DOI: 10.1093/humrep/dev061.

[21] Knez J, Saridogan E, Van Den Bosch T, Mavrelos D, Ambler G, Jurkovic D. ESHRE/ESGE female genital tract anomalies classification system-the potential impact of discarding arcuate uterus on clinical practice. Hum Reprod. 2018 Apr 1;33(4):600-606. DOI: 10.1093/humrep/dey043.

[22] Ludwin A, Ludwin I, Coelho Neto MA, Nastri CO, Bhagavath B, Lindheim SR, Martins WP. Septate uterus according to ESHRE/ESGE, ASRM and CUME definitions: association with infertility and miscarriage, cost and warnings for women and healthcare systems. Ultrasound Obstet Gynecol. 2019 Dec;54(6):800-814. DOI: 10.1002/uog.20291.

[23] RCOG. Guideline: The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage. 2011: 1-18. Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_17.pdf [Accessed: 2021-04-25]

[24] NICE. Guideline: Hysteroscopic metroplasty of a uterine septum for primary infertility.2015:1-8. Availablefrom: https://www.nice.org.uk/guidance/ipg509/resources/hysteroscopic-metroplasty-of-a-uterine-

septum-for-primary-infertility-pdf-1899871693326277 [Accessed: 2021-04-26]

[25] ESHRE Guideline Group on RPL, Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S, Nelen W, Peramo B, Quenby S, Vermeulen N, Goddijn M. ESHRE guideline: recurrent pregnancy loss. Hum Reprod Open 2018; DOI: 10.1093/hropen/ hoy004.

[26] Lavergne N, Aristizabal J, Zarka V, Erny R, Hedon B. Uterine anomalies and in vitro fertilization: what are the results? Eur J Obstet Gynecol Reprod Biol. 1996 Sep;68(1-2):29-34. DOI: 10.1016/0301-2115(96)02459-1.

[27] Tomaževič T, Ban-Frangež H, Virant-Klun I, Verdenik I, Požlep B, Vrtačnik-Bokal E. Septate, subseptate and arcuate uterus decrease pregnancy and live birth rates in IVF/ICSI. Reprod Biomed Online. 2010 Nov;21(5):700-5. DOI: 10.1016/j.rbmo.2010.06.028.

[28] Ozgur K, Isikoglu M, Donmez L, Oehninger S. Is hysteroscopic correction of an incomplete uterine septum justified prior to IVF? Reprod Biomed Online. 2007 Mar;14(3):335-40. DOI: 10.1016/s1472-6483(10)60876-0.

[29] Spanish Infertility SWOT Group (SISG), Checa MA, Bellver J, Bosch E, Espinós JJ, Fabregues F, Fontes J, García-Velasco J, Requena A. Hysteroscopic septum resection and reproductive medicine: A SWOT analysis. Reprod Biomed Online. 2018 Dec;37(6):709-715. DOI: 10.1016/j.rbmo.2018.09.013.

[30] Rikken JFW, Verhorstert KWJ, Emanuel MH, Bongers MY, Spinder T, Kuchenbecker WKH, Jansen FW, van der Steeg JW, Janssen CAH, Kapiteijn K, Schols WA, Torrenga B, Torrance HL, Verhoeve HR, Huirne JAF, Hoek A, Nieboer TE, van Rooij IAJ, Clark TJ, Robinson L, Stephenson MD, Mol BWJ, van der Veen F, van Wely M, Goddijn M. Septum resection in women with a septate uterus: a cohort study. Hum Reprod. 2020 Jul 1;35(7):1578-1588. DOI: 10.1093/humrep/dez284. Erratum in: Hum Reprod. 2020 Jul 1;35(7):1722.

[31] Rikken JFW, Kowalik CR, Emanuel MH, Bongers MY, Spinder T, Jansen FW, Mulders AGMGJ, Padmehr R, Clark TJ, van Vliet HA, Stephenson MD, van der Veen F, Mol BWJ, van Wely M, Goddijn M. Septum resection versus expectant management in women with a septate uterus: an international multicentre open-label randomized controlled trial. Hum Reprod. 2021 Apr 20;36(5):1260-1267. DOI: 10.1093/humrep/deab037.

[32] Surrey ES, Katz-Jaffe M, Surrey RL, Small AS, Gustofson RL, Schoolcraft WB. Arcuate uterus: is there an impact on in vitro fertilization outcomes after euploid embryo transfer? Fertil Steril. 2018 Apr;109(4):638-643. DOI: 10.1016/j.fertnstert.2017.12.001.

[33] Chen X, Liu P, Sheng Y, Li W, Tang R, Ding L, Qin Y, Chen ZJ. The impact of unicornuate uterus on perinatal outcomes after IVF/ICSI cycles: a matched retrospective cohort study. J Matern Fetal Neonatal Med. 2019 Aug;32(15):2469-2474. DOI: 10.1080/14767058.2018.1438403.

[34] Hur C, Rehmer J, Flyckt R, Falcone T. Uterine Factor Infertility: A Clinical Review. Clin Obstet Gynecol. 2019 Jun;62(2):257-270. DOI: 10.1097/GRF.0000000000000448.

[35] Coughlan C, Ledger W, Wang Q, Liu F, Demirol A, Gurgan T, Cutting R, Ong K, Sallam H, Li TC. Recurrent implantation failure: definition and management. Reprod Biomed Online. 2014 Jan;28(1):14-38. DOI: 10.1016/j.rbmo.2013.08.011.

[36] Tao Z, Duan H. [Expression of adhesion-related cytokines in the

uterine fluid after transcervical resection of adhesion]. Zhonghua Fu Chan Ke Za Zhi. 2012 Oct;47(10):734-7. Chinese. PMID: 23302729.

[37] Demirol A, Gurgan T. Effect of treatment of intrauterine pathologies with office hysteroscopy in patients with recurrent IVF failure. Reprod Biomed Online. 2004 May;8(5):590-4. DOI: 10.1016/s1472-6483(10)61108-x.

[38] Doroftei B, Dabuleanu AM, Ilie OD, Maftei R, Anton E, Simionescu G, Matei T, Armeanu T. Mini-Review of the New Therapeutic Possibilities in Asherman Syndrome-Where Are We after One Hundred and Twenty-Six Years? Diagnostics (Basel). 2020 Sep 17;10(9):706. DOI: 10.3390/diagnostics10090706.

[39] Seshadri S, El-Toukhy T, Douiri A, Jayaprakasan K, Khalaf Y. Diagnostic accuracy of saline infusion sonography in the evaluation of uterine cavity abnormalities prior to assisted reproductive techniques: a systematic review and meta-analyses. Hum Reprod Update. 2015 Mar-Apr;21(2):262-74. DOI: 10.1093/humupd/dmu057.

[40] Sylvestre C, Child TJ, Tulandi T, Tan SL. A prospective study to evaluate the efficacy of two- and three-dimensional sonohysterography in women with intrauterine lesions. Fertil Steril. 2003 May;79(5):1222-5. DOI: 10.1016/s0015-0282(03)00154-7.

[41] Makris N, Kalmantis K, Skartados N, Papadimitriou A, Mantzaris G, Antsaklis A. Three-dimensional hysterosonography versus hysteroscopy for the detection of intracavitary uterine abnormalities. Int J Gynaecol Obstet. 2007 Apr;97(1):6-9. DOI: 10.1016/j.ijgo.2006.10.012.

[42] Yu D, Wong YM, Cheong Y, Xia E, Li TC. Asherman syndrome--one century later. Fertil Steril. 2008 Apr;89(4):759-79.DOI: 10.1016/j.fertnstert.2008.02.096.

[43] Zikopoulos KA, Kolibianakis EM, Platteau P, de Munck L, Tournaye H, Devroey P, Camus M. Live delivery rates in subfertile women with Asherman's syndrome after hysteroscopic adhesiolysis using the resectoscope or the Versapoint system. Reprod Biomed Online. 2004 Jun;8(6):720-5. DOI: 10.1016/s1472-6483(10)61654-9.

[44] Khan Z, Goldberg JM. Hysteroscopic Management of Asherman's Syndrome. J Minim Invasive Gynecol. 2018 Feb;25(2):218-228. DOI: 10.1016/j.jmig.2017.09.020.

[45] Doroftei B, Dabuleanu AM, Ilie OD, Maftei R, Anton E, Simionescu G, Matei T, Armeanu T. Mini-Review of the New Therapeutic Possibilities in Asherman Syndrome-Where Are We after One Hundred and Twenty-Six Years? Diagnostics (Basel). 2020 Sep 17;10(9):706. DOI: 10.3390/diagnostics10090706.

[46] Benor A, Gay S, DeCherney A. An update on stem cell therapy for Asherman syndrome. J Assist Reprod Genet. 2020 Jul;37(7):1511-1529. DOI: 10.1007/s10815-020-01801-x

[47] Tan J, Li P, Wang Q, Li Y, Li X, Zhao D, Xu X, Kong L. Autologous menstrual blood-derived stromal cells transplantation for severe Asherman's syndrome. Hum Reprod. 2016 Dec;31(12):2723-2729. DOI: 10.1093/humrep/dew235.

[48] Orhue AA, Aziken ME, Igbefoh JO. A comparison of two adjunctive treatments for intrauterine adhesions following lysis. Int J Gynaecol Obstet. 2003 Jul;82(1):49-56. DOI: 10.1016/s0020-7292(03)00030-4.

[49] Aghajanova L, Cedars MI, Huddleston HG. Platelet-rich plasma in the management of Asherman

syndrome: case report. J Assist Reprod Genet. 2018 May;35(5):771-775. DOI: 10.1007/s10815-018-1135-3.

[50] Fernandez H, Al-Najjar F, Chauveaud-Lambling A, Frydman R, Gervaise A. Fertility after treatment of Asherman's syndrome stage 3 and 4. J Minim Invasive Gynecol. 2006 Sep-Oct;13(5):398-402. DOI: 10.1016/j.jmig.2006.04.013.

[51] Brinsden PR. Gestational surrogacy. Hum Reprod Update. 2003 Sep-Oct;9(5):483-91. DOI: 10.1093/humupd/dmg033.

[52] Sharma S, Bathwal S, Agarwal N, Chattopadhyay R, Saha I, Chakravarty B. Does presence of adenomyosis affect reproductive outcome in IVF cycles? A retrospective analysis of 973 patients. Reprod Biomed Online. 2019 Jan;38(1):13-21. DOI: 10.1016/j.rbmo.2018.09.014.

[53] Upson K, Missmer SA. Epidemiology of Adenomyosis. Semin Reprod Med. 2020 May;38(2-03):89-107. DOI: 10.1055/s-0040-1718920. Epub 2020 Oct 26.

[54] Dueholm M. Uterine adenomyosis and infertility, review of reproductive outcome after in vitro fertilization and surgery. Acta Obstet Gynecol Scand. 2017 Jun;96(6):715-726. DOI: 10.1111/aogs.13158.

[55] Safari S, Faramarzi A, Agha-Rahimi A, Khalili MA. Live birth in a woman with recurrent implantation failure and adenomyosis following transfer of refrozen-warmed embryos. Clin Exp Reprod Med. 2016 Sep;43(3):181-4. DOI: 10.5653/cerm.2016.43.3.181

[56] Vannuccini S, Petraglia F. Recent advances in understanding and managing adenomyosis. F1000Res. 2019 Mar 13;8:F1000 Faculty Rev-283. DOI: 10.12688/f1000research.17242.1.

[57] Chapron C, Vannuccini S, Santulli P, Abrão MS, Carmona F, Fraser IS, Gordts S, Guo SW, Just PA, Noël JC, Pistofidis G, Van den Bosch T, Petraglia F. Diagnosing adenomyosis: an integrated clinical and imaging approach. Hum Reprod Update. 2020 Apr 15;26(3):392-411. DOI: 10.1093/humupd/dmz049.

[58] Tremellen KP, Russell P. The distribution of immune cells and macrophages in the endometrium of women with recurrent reproductive failure. II: adenomyosis and macrophages. J Reprod Immunol. 2012 Jan;93(1):58-63. DOI: 10.1016/j.jri.2011.12.001.

[59] Meredith SM, Sanchez-Ramos L, Kaunitz AM. Diagnostic accuracy of transvaginal sonography for the diagnosis of adenomyosis: systematic review and metaanalysis. Am J Obstet Gynecol. 2009 Jul;201(1):107.e1-6. DOI: 10.1016/j.ajog.2009.03.021.

[60] Bazot M, Daraï E. Role of transvaginal sonography and magnetic resonance imaging in the diagnosis of uterine adenomyosis. Fertil Steril. 2018 Mar;109(3):389-397. DOI: 10.1016/j.fertnstert.2018.01.024

[61] Tamai K, Koyama T, Umeoka S, Saga T, Fujii S, Togashi K. Spectrum of MR features in adenomyosis. Best Pract Res Clin Obstet Gynaecol. 2006 Aug;20(4):583-602. DOI: 10.1016/j.bpobgyn.2006.01.009.

[62] Exacoustos C, Manganaro L, Zupi E. Imaging for the evaluation of endometriosis and adenomyosis. Best Pract Res Clin Obstet Gynaecol. 2014 Jul;28(5):655-81. DOI: 10.1016/j.bpobgyn.2014.04.010.

[63] Yoldemir T. Adenomyosis and fertility outcomes. Gynecol Endocrinol. 2020 Jun;36(6):473-474. DOI: 10.1080/09513590.2020.1773426.

[64] Tremellen K, Russell P. Adenomyosis is a potential cause of recurrent implantation failure during IVF treatment. Aust N Z J Obstet Gynaecol. 2011 Jun;51(3):280-3. DOI: 10.1111/j.1479-828X.2010.01276.x.

[65] Hou X, Xing J, Shan H, Mei J, Sun Y, Yan G, Sun H, Wang J. The effect of adenomyosis on IVF after long or ultra-long GnRH agonist treatment. Reprod Biomed Online. 2020 Nov;41(5):845-853. DOI: 10.1016/j.rbmo.2020.07.027.

[66] Pontis A, D'Alterio MN, Pirarba S, de Angelis C, Tinelli R, Angioni S. Adenomyosis: a systematic review of medical treatment. Gynecol Endocrinol. 2016 Sep;32(9):696-700. DOI: 10.1080/09513590.2016.1197200.

[67] He Y, Wu H, He X, Xing Q, Zhou P, Cao Y, Wei Z. Administration of atosiban in patients with endometriosis undergoing frozen-thawed embryo transfer: a prospective, randomized study. Fertil Steril. 2016 Aug;106(2):416-22. DOI: 10.1016/j.fertnstert.2016.04.019.

[68] Ng EH, Li RH, Chen L, Lan VT, Tuong HM, Quan S. A randomized double blind comparison of atosiban in patients undergoing IVF treatment. Hum Reprod. 2014 Dec;29(12):2687-94. DOI: 10.1093/humrep/deu263.

[69] Palagiano A, Cozzolino M, Ubaldi FM, Palagiano C, Coccia ME. Effects of Hydrosalpinx on Endometrial Implantation Failures: Evaluating Salpingectomy in Women Undergoing in vitro fertilization. Rev Bras Ginecol Obstet. 2021 Apr;43(4):304-310. English. DOI: 10.1055/s-0040-1722155.

[70] Capmas P, Suarthana E, Tulandi T. Management of Hydrosalpinx in the Era of Assisted Reproductive Technology: A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 2021 Mar;28(3):418-441. DOI: 10.1016/j.jmig.2020.08.017.

[71] Strandell A, Lindhard A, Waldenström U, Thorburn J, Janson PO, Hamberger L. Hydrosalpinx and IVF outcome: a prospective, randomized multicentre trial in Scandinavia on salpingectomy prior to IVF. Hum Reprod. 1999 Nov;14(11):2762-9. DOI: 10.1093/humrep/14.11.2762.

[72] Practice Committee of the American Society for Reproductive Medicine. Committee opinion: role of tubal surgery in the era of assisted reproductive technology. Fertil Steril. 2012 Mar;97(3):539-45. DOI: 10.1016/j.fertnstert.2011.12.031.

[73] Den Hartog JE, Morré SA, Land JA. Chlamydia trachomatis-associated tubal factor subfertility: Immunogenetic aspects and serological screening. Hum Reprod Update. 2006 Nov-Dec;12(6):719-30. DOI: 10.1093/humupd/dml030.

[74] Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile female: a committee opinion. Fertil Steril. 2015 Jun;103(6):e44-50. DOI: 10.1016/j.fertnstert.2015.03.019. Epub 2015 Apr 30.

[75] Coppus SF, Opmeer BC, Logan S, van der Veen F, Bhattacharya S, Mol BW. The predictive value of medical history taking and Chlamydia IgG ELISA antibody testing (CAT) in the selection of subfertile women for diagnostic laparoscopy: a clinical prediction model approach. Hum Reprod. 2007 May;22(5):1353-8. DOI: 10.1093/humrep/del521.