

Hysteroscopy and ART: Defying Clinical Indications Based on Current Evidence

Fani Gkrozou^{1*}, Dimitrios Bouras-Soulimas², Vasileios Bais¹, Nikoleta Koutalia¹, Dimitrios Lentzaris¹, Anastasia Vatopoulou¹, Chara Skentou¹, Minas Paschopoulos¹ and Angelos Daniilidis³

¹Department of Obstetrics and Gynaecology, Medical School, University of Ioannina, Greece.

²Laconia General Hospital - Molaoi Nursing Unit, Greece.

³Department of Obstetrics and Gynaecology, Medical School, Aristotle University of Thessaloniki, Greece.

*Correspondence:

Fani Gkrozou, Assistant Professor, Department of Obstetrics and Gynaecology, Medical School, University of Ioannina, Greece.

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ABSTRACT

Embryo's Implantation is a question that we are not in the position to answer in full details. We know that it depends on embryo's quality and uterine receptivity. It is possible to access uterine cavity before in vitro fertilisation by a variety of tools, however hysteroscopy is the gold standard in evaluation of uterine cavity and potential pathology. The frequencies of unrecognised uterine pathology revealed by hysteroscopy are 18-50% and 40-43% in patients undergoing in vitro fertilisation or after recurrent implantation failure respectively. Data is inconclusive regarding the role of hysteroscopy on pregnancy outcome after ART. This review aims to evaluate the validity of office hysteroscopy in sub fertile population before or after at least one failed fertility IVF treatment.

Keywords

Hysteroscopy, Assisted conception, Recurrent implantation failure, Live birth, Assisted conception, Endometrial pathology, Unexplained subfertility.

Background

An increased prevalence of fertility issues, has been well documented and more people are seeking medical help in a fertility unit. In European countries, the current prevalence of infertility is estimated to be 8-14% and about one in six couples is estimated to face delays in conception [1,2]. Roughly 15% of couples referred to fertility clinics are affected by unexplained infertility [3], the respective percentage of people classified as subfertile for unexplained reasons rises up to 30% [4]. This variable incidence reflects different selection criteria applied and discrepancies regarding female age in the enrolled groups of patients [3,5,6].

Consequently, several therapeutic approaches has been employed in order to treat unexplained infertility, such as intracytoplasmic sperm injection (ICSI) and *in vitro* fertilisation (IVF) treatment, which are widely used. In 2021, over 400.000 reproductive

technology (ART) procedures have been reported in the United States alone, whereas in 2018, the number did not exceed 205.000 [7,8]. ART is any fertility related treatment in which eggs or embryos are manipulated [9]. Despite technological advances and the steadily increasing number of artificial cycles worldwide, the success rate of IVF cycles remains low [8]. Only one third of these procedures result in live birth (approximately 30%) and a significant proportion of IVF cycles results in implantation failure [1,10].

Infertility is admittedly an upsetting and distressing life experience to patients which is accompanied by significant mental implications and overall low Quality of Life (QoL) [11]. As expected, in cases experiencing recurrent implantation failure (RIF) the beforementioned mental impact is even more profound. To date, there is a lack of consensus regarding the definition of RIF [10,12-16] and is usually described as 'three or more failed treatment cycles' or 'two or more failed treatment cycles'. Recent literature defines RIF as the absence of implantation after at least two consecutive treatment cycles irrespective of the transfer of good quality and of appropriate developmental stage embryos [10,17]. Embryonic loss

occurring repeatedly after assisted reproduction, may be attributed to many factors and these can be grouped into three categories: a. reduced endometrial receptivity (uterine cavity abnormalities, inadequate endometrial thickness, altered expression of adhesive molecules, immunological causes, thrombophilia), b. embryonic defects (chromosomal abnormalities, suboptimal culture conditions) and c. multifactorial causes (endometriosis, presence of hydrosalpinges, suboptimal ovarian stimulation) [14,15,18].

Evaluation of intrauterine cavity is performed by Transvaginal ultrasonography (TVS), saline infusion sonography (SIS), hysterosalpingography (HSG) and hysteroscopy [19-22]. Hysteroscopy allows direct visualization of the uterine cavity and the cervical canal, providing the opportunity to perform surgical treatment in the same setting [23-25]. The most common indications for hysteroscopy are abnormal uterine bleeding, abnormal endometrial thickness and mullerian congenital anomalies [26]. Repeated IVF failures have become another indication for performing hysteroscopy [27]. Uterine cavity abnormalities, such as polyps, intrauterine adhesions, septae and submucous fibroids, have been found in 10% to 15% of women seeking treatment for fertility problems, which requires a surgical approach [28,29]. 50% of women with repeated implantation failure have various hysteroscopic patterns, without being able to recognise a specific pathology [23-35]. Although hysteroscopy is acknowledged as the 'gold standard' for the identification and treatment of endometrial pathology, its place in the evaluation of subfertility remains debatable [36]. According to the Royal College of Obstetricians and Gynaecologists (RCOG), hysteroscopy should be offered when clinically indicated but not in the context of initial fertility assessment [2]. A similar approach has been adopted by ESHRE too [37].

Taken all this into consideration, the aim of the present review is to investigate the role of hysteroscopy in women with at least one failed IVF cycle; to determine whether hysteroscopy in women with at least one failed IVF cycle is of any clinical significance and therefore can improve outcome. In the same time, we will try to evaluate hysteroscopy in the assessment of uterine pathologies in infertile women experiencing RIF and explore whether any intervention improves pregnancy rates in this population.

Materials and Methods

For this project, three major search engines were included: PubMed, MEDLINE and Embase. Further search on Cochrane Library Registry for reviews, clinical trials and meta-analysis on hysteroscopy and ART was also conducted. The following key-words were used to complete our search: 'hysteroscopy' AND '*in-vitro* fertilization failure' OR 'IVF failure' OR 'embryoimplantation' OR 'embryo implantation failure'. Besides the retrieved studies, their reference lists were screened as well, to identify other related studies not captured by electronic searches. The language of publication was restricted to English. Inclusion criteria included studies addressing infertility in patients undergoing any type of ART and hysteroscopy before or at least after one failed IVF cycle. The search was focused on studies providing data on pregnancy outcomes. Study exclusion criteria

were: studies referred to patients' after their first IVF/ICSI cycle, with no history of RIF, studies where data on pregnancy outcomes is missing or not provided and finally studies designed to assess the efficacy of hysteroscopy and associated scratching.

Role of Hysteroscopy at Infertile Women Before ART Treatment

Results are very controversial when hysteroscopy before IVF treatment is studied. Some authors support that whenever endometrial pathology is not diagnosed by pelvic ultrasound or hysterosalpingography hysteroscopy before first IVF does not improve live birth rate [38]. Nevertheless, other authors like Abid et al. noticed 10.7 % improvement in ongoing pregnancy rate but without any statistical significance [39]. A systematic review and meta-analysis, which included 10 randomized controlled trials involving 3612 patients, assessed the effect of outpatient hysteroscopy before ART. All patients had been confirmed to have no major uterine abnormalities through normal transvaginal sonography or hysterosalpingography prior to ART. The analysis found that undergoing outpatient hysteroscopy before ART was associated with a significant improvement in LBR and CPR. A subgroup analysis within the meta-analysis found no significant difference in clinical pregnancy rates based on hysteroscopy findings [40].

Even scientific national societies recommendations vary, mainly because evidence is of poor quality or large heterogeneity. The ESHRE guidelines do not recommend hysteroscopy before first IVF. More specifically ESHRE mentions that "Hysteroscopy should be offered if intrauterine pathology is suspected by transvaginal ultrasound (TVUS). Hysteroscopy should not be routinely offered to infertile women who have normal TVUS findings. In women who have normal TVUS findings and are undergoing IVF, hysteroscopy does not improve the outcome" [37]. Moreover, it has been shown that many unsuspected intra-uterine pathologies were detected by hysteroscopy after RIF reaching 11-45% [41,42]. A meta-analysis by Pundir et al. proved that LBR increased after hysteroscopy before women go for a first IVF cycle [43]. These results though are controversial because most studies included were non-randomized [43].

Role of Hysteroscopy in Women Undergoing at Least One Failed IVF cycles

In 2020, Okohue et al. reported that 76.6% of women with normal ultrasound findings after two previous failed IVF cycles had no pathology on hysteroscopy. Following the procedure, there was a 31.2% clinical pregnancy rate (CPR), whereas 37.6% had failed IVF cycles and 31.2% were lost to follow-up [44].

In a prospective study from Saudi Arabia, hysteroscopy was performed on 266 women with at least 2 implantation failures RIF; in 39.1% there were one or more abnormal hysteroscopic findings. More specifically, women were found to have endometrial adhesions, polyps, submucosal fibroids, indication of chronic endometritis and uterine malformations, whereas preceding hysterosalpingography (HSG) was able to detect only half of them. The study showed no statistically significant difference

in fertilization rate, when the two groups with and without hysteroscopic anomalies were compared [45]. Gao et al. [46] reported a similar prevalence (37.13%) of hysteroscopy findings, with the most common abnormalities being endometrial polyps or polypoid endometrium (19.16%), endometrial hyperplasia (5.99%) and adhesions (4.49%); 79.03% of these findings had not been detected in previous HSG or TVS examinations. The CPR and implantation rates were significantly higher in all women that underwent hysteroscopy, even in patients without uterine abnormalities, *without being able to dictate a probable reason* [46]. Moini et al. agreed with previous authors. This study reported a similar percentage (33.6%) of uterine cavity abnormalities, that hadn't been revealed before hysteroscopy, however no significant difference in pregnancy rate between women that were treated by hysteroscopy for a detected abnormality and those who had normal findings [33]. These studies concluded that hysteroscopy is able to recognise better endometrial pathology. Even if this is treated or not according to authors the CPR will be increased but not significantly. The same result was showed by Pabuçcu et al. on the other hand, reported that 51.2% of women had uterine cavity abnormalities on hysteroscopy, but the LBRs of women with abnormal hysteroscopic findings, with normal findings and without having undergone hysteroscopy were similar [47].

In the contrary, a study from Cao et al. showed that outpatient hysteroscopy (OH) in women with at least two implantation failures and normal TVS or HSG assessment, had CPR and LBR significantly higher. At this study though, there was no difference in either CPR or LBR between the normal and abnormal hysteroscopy groups. Subgroup analysis also showed a significant association between OH and CPR in Asia, but not in Europe. Five of the studies included reported abnormal hysteroscopy findings; the most common of those being polyps (16.47%), endometrial adhesions (10.6%) and chronic endometritis (3.89%). The findings suggest that hysteroscopy-related endometrial injury may play a significant role in improving pregnancy outcomes. This effect is likely due to an inflammatory response involving numerous macrophages and cytokines, which promotes decidualization and prepares the endometrium for embryo implantation [48].

The TROPHY RCT randomized 702 women with two to four failed IVF cycles and normal TVS to either have OH or no hysteroscopy a month before the subsequent treatment cycle. The results showed that OH does not improve live birth rate (LBR) and there were no significant differences in pregnancy, implantation or miscarriage rates. Hysteroscopy revealed cervical or uterine cavity abnormalities in 26% of women. However, in two-thirds of these hysteroscopies, the abnormalities were not treated as they were considered of undetermined clinical significance; therefore, the role of hysteroscopy in treatment of specific uterine cavity abnormalities, like arcuate uterine cavity, short cervical canal or any subtle endometrial abnormality, hasn't been assessed [49]. This result is controversial when is compared with studies that report improvement of CPR at women after at least two implantation failures that had diagnostic hysteroscopy or hysteroscopically treated endometrial pathology [23,50,51]. Contrary evidence was

provided by another RCT, which showed improved pregnancy outcomes in the hysteroscopy group, irrespective of the presence of endometrial pathology. The key difference in this study was the identification of a high rate of intrauterine abnormalities via hysteroscopy (37.25%) [38].

The positive effect of hysteroscopy on ART outcomes may result from detecting and treating intrauterine pathologies. However, even in cases with normal hysteroscopy findings, pregnancy rates in various studies were higher, highlighting additional benefits for improved implantation rates such as endometrial injury, immune response activation with subsequent growth factors and cytokines release. Some studies also suggest that local endometrial injury by hysteroscopy during ovarian stimulation alters endometrial mRNA expression and increases implantation rates [50].

Role of Hysteroscopy at Infertile Women without Intrauterine Pathologies

Yang et al. [52] supported that diagnostic hysteroscopy can improve CPR and LBR before IVF/ICSI even at women without intrauterine pathology, especially in cases of RIF. At this study, a subgroup analysis took place, to identify if endometrial stimulation was performed during hysteroscopy and to measure if endometrial biopsy improves reproductive outcomes at this group of population without intrauterine pathology. Hysteroscopy group didn't show any improvement regardless of the endometrial stimulation, when it was compared with the non-hysteroscopy group.

Ghasemi et al. conducted an RCT including 228 women with primary infertility and normal TVUS and HSG before their first IVF cycle. The women in the first group underwent hysteroscopy and irrigation of the uterine cavity prior to their first ART whereas in the second they did not. If uterine anomalies were detected during the hysteroscopy the women were excluded from the study. The hysteroscopy group showed a significantly higher cumulative LBR (44.05%) compared to the no hysteroscopy group (32.25%) [53]. In another randomized controlled trial by Berntsen et al., 184 women with at least one previous failed IVF/ICSI cycle and no intrauterine abnormalities were assigned to either an office hysteroscopy with endometrial scratch injury group or a control group. The results indicated a non-significant increase in positive serum hCG, ongoing pregnancy, and live birth rates in the hysteroscopy group [54].

Role of Hysteroscopy at Infertile Women Without Intrauterine Pathologies

Septum

Uterine septum is the most prevalent congenital anomaly of reproductive system. Numerous studies have demonstrated a link between uterine septum and elevated risks of miscarriage, recurrent pregnancy loss, and preterm delivery. The role of uterine septum in infertility, as well as the indications for septum resection remains controversial [1,2]. A retrospective cohort study included 269 patients with secondary infertility and uterine septum. The first group underwent hysteroscopic septum resection prior to ART, while the second group, proceeded with ART without septum

resection. Both cumulative pregnancy rate (71.0% vs. 59%, $P = 0.044$) and cumulative live birth rate (54.4% vs. 44%, $P = 0.098$) were higher in surgical group compared to the control group, with a statistically significant difference noted [2]. Another meta-analysis of 2022 evaluated pregnancy outcomes in women who underwent hysteroscopic septum resection compared to those who received no intervention. The findings indicated no significant difference in pregnancy rates. However, the live birth rate was notably higher in the group that underwent septum resection [3]. The method of hysteroscopic septum removal, whether using scissors or a resectoscope, showed no statistically significant difference in reproductive outcomes [4].

Endometrial polyps

Endometrial polyps are localized overgrowths of endometrium, composed of endometrial glands, stroma, and blood vessels. The prevalence of endometrial polyps among asymptomatic infertile women undergoing diagnostic hysteroscopy prior to IVF is reported to be between 6% and 32% [5]. The association between endometrial polyps and infertility has been the subject of extensive research, yet it still remains controversial [5,6]. A systematic review published in 2019, which included eight studies, compared hysteroscopic polypectomy with no intervention prior to ART. The results indicated that hysteroscopic resection of endometrial polyps was associated with a higher rate of clinical pregnancy in patients undergoing intrauterine insemination (IUI). However, no significant benefits were observed in terms of clinical pregnancy, live birth, miscarriage, or implantation rates for patients undergoing IVF/ICSI cycles. The small number of studies included, variations in study design, and the absence of randomized controlled trials may have restricted the ability to draw valid conclusions about the impact of hysteroscopic polypectomy on IVF outcomes. As results, the effect of hysteroscopic polypectomy on pregnancy outcomes of patients undergoing ART remains uncertain [7].

Leiomyomas

Uterine leiomyomas are benign smooth muscle tumors of the uterus present in 5–10% of women experiencing infertility. In 1–3% of these cases, leiomyomas are the sole cause of infertility [8]. Various theories have been proposed to explain how they may affect fertility, with the most prominent being changes to local anatomy due to the anatomic distortion of the endometrial cavity. Functional alterations have also been implicated, such as increased uterine contractility and persistent endometrial inflammation [9]. A meta-analysis comparing reproductive outcomes in women undergoing ART with and without leiomyomas found that submucosal lesions significantly reduced reproductive outcomes, with an OR (95% CI) of 0.3 (0.1–0.7) for conception and 0.3 (0.1–0.8) for delivery [10]. Although the impact of intramural myomas was less severe, it remained statistically significant, with an OR (95% CI) of 0.8 (0.6–0.9) for conception and 0.7 (0.5–0.8) for delivery. In contrast, subserosal lesions did not appear to affect reproductive outcomes [10]. Women with submucosal leiomyomas experience lower chances of conception, significantly higher miscarriage rates, and reduced live birth rates, regardless of the method of conception. Hysteroscopic removal of these fibroids

has been shown to improve fertility potential and IVF outcomes. Consequently, surgical intervention is reasonably recommended for women seeking to conceive [9].

Diagnostic Hysteroscopy Performed Before Fresh and Frozen-Thawed Embryo Transfer in IVF Cycles on Reproductive Outcomes

Eserol et al. has shown that performing diagnostic hysteroscopy before fresh or frozen-thawed embryo does not make any difference in pregnancy rates [55]. This data is in agreement with Kamath et al. They investigated the feasibility of routine hysteroscopy at the early stage of investigation of fertility or before intrauterine insemination [56]. After reviewing 11 publications, they concluded that there was not strong evidence to support hysteroscopy as a screening method in sub-fertile women with a normal basic fertility work-up for increasing live birth and clinical pregnancy rates [57].

Role of Hysteroscopy at Women with Unexplained Infertility

Unexplained subfertility is still a mystery. Our knowledge on this matter is very limited. There are cases that hysteroscopy can reveal unknown intrauterine pathologies like endometrial polyps, fibroids, septa, or intrauterine adhesions that may have been missed by transvaginal ultrasound [19]. Treatment of intrauterine pathology is possible by performing operative hysteroscopy too [58]. It is not known though if treatment or repair of these pathologies can make improve uterine receptivity and pregnancy outcome of this group of population. Only one randomised control study (RCT) can be found in literature on that matter, published by Seyam et al. and included 200 women. Ongoing pregnancy was reported in primary study report. Once hysteroscopy is offered at women with unexplained subfertility, even without any ultrasound indication, will result to pregnancy with a range of 23 to 81%. The evidence was graded as very low quality. However, there were statistically significant differences between the intervention (screening hysteroscopy) and control group (no hysteroscopy) for secondary outcomes like clinical pregnancy rate and miscarriage rate, where hysteroscopy group had improved results. As consequence, it is safe to conclude that existed evidence is not enough to offer hysteroscopy in every woman with unexplained subfertility who are trying to conceive spontaneously.

Conclusion

A lack of consensus of reproductive outcomes following hysteroscopy after ART failure is noted among the existing studies. Hysteroscopy in women with implantation failures have failed to improve LBR. No significant difference in implantation rates is reported by most of studies. No study reports a significant difference in miscarriage rate too. As result, clinicians shouldn't offer diagnostic hysteroscopy to every woman without indication of uterine pathology and infertility.

Some authors have examined the value of routine hysteroscopy before the first IVF cycle. Results have been controversial and more prospective studies are necessary to be conducted. Similar are outcomes of studies about CPR, where some authors reported an improved CPR in women with corrected uterine pathology.

Other studies though, showed no significant difference in either CPR or LBR between women with normal or abnormal findings at hysteroscopy.

In conclusion, hysteroscopy is a reliable diagnostic tool that can detect intrauterine pathologies missed by other imaging modalities; correction of these abnormalities it has not been proved to improve pregnancy outcomes in women with implantation failures. However, more prospective studies are needed to investigate the role of hysteroscopy in patients with ART treatment failures.

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