Review

Hysteroscopy and ART: Defying Clinical Indications Based on Current Evidence

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Hysteroscopy and ART: Defying Clinical Indications Based on Current Evidence

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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 in vitro fertilisation. This review aims to evaluate the validity of office hysteroscopy in subfertile population before or after 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% [1,2] and about one in six couples is estimated to face delays in conception [1]. Roughly 10% 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 37% [4]. This variable incidence reflects different selection criteria applied and discrepancies regarding female age in the enrolled groups of patients [3,5–7].

Consequently, several therapeutic approaches has been employed in order to treat unexplained subfertility, such as intracytoplasmic sperm injection (ICSI) and in vitro fertilisation (IVF) treatment, which are widely used. In 2018, over 200.000 assisted reproductive technology (ART) procedures have been reported in the United States alone, whereas in 2006, the number did not exceed 140.000 [8,9]. 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].

Subfertility 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 before mentioned 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

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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) [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 [23,30–35]. 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 'embryo implantation' 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 subfertility in patients undergoing IVF treatment (with or without ICSI) and the therapeutic intervention was hysteroscopy after at least 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 in Women Undergoing at least Two 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 [38].

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

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anomalies were compared [39].Gao et al [40]. 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* [40].Moini et al. agreed with previous authors. This studuy 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 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 [41].

In the contrary, there is 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%) [42,43].

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 [44]. 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 [23,45,46].[47]

In 2004, a study randomized a total of 421 women with two or more failed IVF cycles and normal HSG into two groups. One had hysteroscopy and the other did not. CPR was significantly different between these two groups of population irrespectively of the presence of endometrial pathology, diagnosed by hysteroscopy [48]. Another RCT that studied population with and without hysteroscopy had similar outcome, but with the key difference of calculating a higher percentage of intrauterine abnormalities detected by hysteroscopy(37.25%) [49].These two RCTs also indicate higher pregnancy rates in RIF patients who had hysteroscopy, but no pathology was detected [48,49]. Similar results are supported by Oliviera et al., who reported significantly higher pregnancy rates in women who were treated for uterine cavity abnormalities compared to women with normal findings on hysteroscopy [32].

Role of Hysteroscopy at Infertile Women without Intrauterine Pathologies

Yang et al [50].supported that diagnostic hysteroscopy can improve CPR and LBR before IVF/ICSI even at women without intrauterine pathology, especially in cases of RIF, even though hysteroscopy before the first IVF attempt does not seem to improve the outcome. 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.

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A study from Takahashi et al. had same outcomes as the above-mentioned study. In addition, though, they concluded that LBR is improved when hysteroscopy is performed before IVF/ICSI for women with RIF, even without endometrial pathology, but once hysteroscopy is performed before the first IVF, there is no difference [51].

Role of Hysteroscopy at Infertile Women before IVF 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 hysterosalpingographyhysteroscopy before first IVF does not improve live birth rate [49].Nevertheless, other authors like Abid et al. noticed 10.7 % improvement in ongoing pregnancy rate but without any statistical significance [52].

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% [43,53,54]A meta-analysis by Pundir et al. proved that LBR increased after hysteroscopy before women go for a first IVF cycle [55]. These results though are controversial because most studies included were non-randomized [55].

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[56]. This data is in agreement with Kamath e t al. They investigated the feasibility of routine hysteroscopy at the early stage of investigation of fertility or before intrauterine insemination[57]. 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 Subfertility

Unexplained subfertility is still a mystery. Our knowledge on this matter is very imitated. 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 [59] 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.

Conclusions

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

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improve the LBR. No significant difference in implantation rates is reported by most of the studies. No study reports a significant difference in miscarriage rate too.

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 contacted.

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 LBRbetween 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 seems to improve pregnancy outcomes in women with implantation failures. However, more prospective studies are needed to investigate the role of hysteroscopy in patients with IVF treatment failures.

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