

*Opinion***Role of Hysteroscopy on Infertility: The Eternal Dilemma**

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Abstract

Hysteroscopy is the gold standard tool for endoscopic visualization of the uterine cavity and it assesses a simultaneous detection and treatment of intracavitary anomalies with greater accuracy than other methods. The most common uterine abnormalities, including endometrial polyps, submucosal myomas, uterine septum and intrauterine adhesions, are common in infertile women. It is object of debate whether diagnostic and/or operative hysteroscopy should be considered in the basic work-up of infertile couples.

Keywords: hysteroscopy; infertility; endometrial polyp; uterine myoma; intrauterine adhesion; uterus septum

1. Introduction

According to the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization's (WHO), infertility is "the disease of the reproductive system, defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse" [1]. The standard fertility work-up includes tests for ovulation and semen analysis, evaluation of tubal patency by techniques including hysterosalpingography (HSG) or sonohysterography, and transvaginal sonography (TVS). Generally, diagnostic laparoscopy and hysteroscopy are not included in the initial infertility evaluation. In particular, laparoscopy is considered for the diagnosis and treatment of long-term infertility to preclude the existence of peritubal adhesions and endometriosis disease [2,3]. Hysteroscopy is considered the gold standard tool for the endoscopic visualization of the uterine cavity. Office-based operative hysteroscopy is usually well tolerated by patients [4], avoiding most of the uterine traumatic maneuvers and allows a direct approach for the evaluation and treatment of many intrauterine pathologies during the same diagnostic session in a "see and treat" modality [5,6]. Uterine abnormalities are very common in reproductive women and represent approximately 2–3% of causes of infertility, interfering with the normal implantation and placentation [7]. Given the greater diagnostic accuracy of uterine pathologies, hysteroscopy could be indicated in women with unexplained infertility for the detection of disease missed by other tests [8]. Conversely, endoscopic examination of uterine cavity is considered mandatory for the management of infertile women with a diagnosis of intrauterine abnormalities by ultrasound scan [9]. The

most common uterine abnormalities, including endometrial polyps, submucosal myomas, uterine septum and intrauterine adhesions, are detected by hysteroscopy in 10 to 15% of women looking for medical treatment for infertility [10]. The literature of last decades has recognized that the endoscopic treatment of intracavitary increase women fertility.

1.1 Endometrial Polyps

Endometrial polyps represent one of the most frequent causes of abnormal uterine bleeding (AUB) in both pre- and post-menopausal women, but they can be asymptomatic. Transvaginal ultrasound, associated or not with contrast saline infusion or gel installation, should be the primary modality for the detection of endometrial polyps, but the gold standard for diagnosis and treatment is hysteroscopy [11,12]. In women with infertility, a percentage between 15% and 24% of endometrial polyps have been reported. Hysteroscopic approach to remove the endometrial polyps is considered a mini-invasive treatment that can improve pregnancy rates ranging from 23% to 65% [13]. However, the evidence does not currently support the routine polypectomy in infertile women [14]. It should be noted that the location of endometrial polyps could affect infertile status. Therefore, Yanaihara *et al.* [15] found the highest pregnancy rate (57%) after hysteroscopic excision of polyp located in the uterotubal junction, which could cause loss of function of the ostium and affect sperm passage.

1.2 Submucosal Myomas

The incidence of submucosal myomas associated with infertility is estimated between 5% and 10%. Chronic endometrial inflammation, abnormal vascularization, to-



gether with an increased uterine contractility and abnormal local endocrine patterns, are the mechanisms most likely responsible for myomas-associated infertility. The interference with sperm transport or embryo implantation can also be involved [16]. According to retrospective and case control studies, the presence of myomas that protrude into the endometrial cavity decreases pregnancy and implantation rates in patients seeking spontaneous pregnancy or planning to undergo *in vitro* fertilization (IVF). In this perspective, the fertility rate after hysteroscopic myomectomy should increase, especially for large myomas [17].

1.3 Uterine Synechiae

Intrauterine adhesions (IUA), also known as Asherman's Syndrome, are associated with infertility and recurrent pregnancy failure [18,19]. Hysteroscopy represents the better technique for their evaluation, allowing the direct visualization of position, extent and morphology of the adhesion. It is more accurate than other techniques, such as HSG, sonohysterography, TVS and three dimensional-TVS for diagnosis and assists lysis of IUA under direct vision [20]. Hysteroscopic adhesiolysis has been shown to improve fertility rate and conception percentage by up to 48% [21].

1.4 Congenital Uterine Anomalies

Congenital uterine anomalies are caused by defects in the development or fusion of the Mullerian ducts during embryogenesis. The uterus septum is the most frequent uterine malformation, regarding approximately 0.2 to 2.3% of reproductive age women, and it is associated with the highest risk of infertility, pregnancy loss, preterm birth and fetal malpresentation [22]. Hysteroscopic septum resection is the current standard procedure to restore the normal uterine cavity to improve pregnancy outcome [17]. At present, the hysteroscopic resection is recommended by the American Society of Reproductive Medicine (ASRM) guidelines. Conversely, the European Society of Human Reproduction and Embryology (ESHRE), the National Institute for Health and Care Excellence (NICE) and the Royal College of Obstetricians and Gynaecologists (RCOG) do not support the routine use of this procedure [23].

2. Role of Hysteroscopy in the Infertility Work-up

In the assessment of infertility, office hysteroscopy is strongly emerging for its diagnostic and therapeutic capacity of reliable the main intracavitary anomalies [24]. Many uterine diseases, such as endometrial polyps, submucosal myomas, uterine synechiae and congenital malformations, are more common in infertile patients and hysteroscopy has been shown to be able to relieve intrauterine anomalies up to 20–40% of cases with a normal transvaginal ultrasound [8,25]. Whether hysteroscopy should be performed as a part of basic infertility work-up is still

under debate. The Italian Society of Gynecological Endoscopy (ISGE) guidelines recommend hysteroscopy as a part of infertility work-up to evaluate accurately and, at the same time, remove the uterine anomalies. Furthermore, they strongly suggest hysteroscopy in women with recurrent miscarriage and in patients undergoing *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) to evaluate possible uterine disease [25]. This may lead to a decrease of women who make improper use of assisted reproductive techniques and the respective complications (ovarian hyperstimulation syndrome) [26]. However, the National Institute of Health and Clinical Excellence (NICE), the European Society of Human Reproduction and Embryology (ESHRE) and the Royal College of Obstetricians and Gynaecologists (RCOG) do not indicate hysteroscopy as a routine procedure without clinical indications. A recent systematic review of Cochrane Database of Systematic Review analyzed hysteroscopy as a screening procedure in general population of infertile women who desire spontaneous pregnancy or with prior IVF. Studies suggested that the routine use of hysteroscopy in women undergoing IVF may improve clinical pregnancy rate and live birth, but with low-quality evidence. At the same time, there is no high-quality evidence for supporting screening hysteroscopy to implement the reproductive success rate in primary fertility work-up of women with normal TVS or sonohysterography [27]. A second Cochrane review compared operative hysteroscopy and expectant management both in women with intrauterine lesions detected by TVS or other methods and in unexplained subfertility or in women undergoing IVF. The randomized comparison between hysteroscopic myomectomy versus expectant management for unexplained subfertility shows unclear results regarding the improvement of clinical pregnancy (OR (odds ratio) 2.44, 95% CI (confidence interval) 0.97 to 6.17; $p = 0.06$) and miscarriage rates (OR 1.54, 95% CI 0.47 to 5.00; $p = 0.47$) after operative hysteroscopy. Randomized trials involving hysteroscopic polypectomy have not been performed. Conversely, the increase pregnancy rates following hysteroscopic polypectomy has been reliable prior to intrauterine insemination (IUI): OR 4.41, 95% CI 2.45 to 7.96; $p < 0.00001$. Randomized trials about IVF/ICSI have not been performed either [28]. Regarding congenital uterine anomaly, hysteroscopic metroplasty is the gold standard to remove uterine septum. A recent international multicenter cohort study divided 257 women with a septate uterus in a cohort that underwent septum resection ($n = 151$) and a cohort with conservative management ($n = 106$). The results suggest that septum resection does not improve the reproductive outcomes compared with expectant choice in terms of live birth, pregnancy rate and pregnancy loss [29]. These results agree with those of a randomized controlled trial performed the next year. In this work, live birth occurred in 12 of 39 women underwent septum resection and in 14 of 40 women with conservative management (RR (relative risk)

0.88, 95% CI 0.47 to 1.65), raising doubts regard the usefulness of metroplasty to increase reproductive outcomes [20]. It is clear that the effectiveness of operative hysteroscopy as infertility treatment remains an uncertain topic at present.

3. Conclusions

Hysteroscopy is the gold standard for diagnosis and treatment of intrauterine disease and it could be a benefit in women with infertility or recurrent pregnancy loss. Some evidence and guidelines support hysteroscopy as a screening procedure in the infertility work-up, but other do not suggest this procedure in absence of clinical indications. Further research is needed to evaluate the effectiveness of diagnostic and/or operative hysteroscopy for the improvement of reproductive outcomes in women with unexplained subfertility caused by suspected uterine cavity abnormalities or prior to IUI or IVF.

Author Contributions

MG, FAG and GGI: conceptualization and writing (original draft); MC, VD, ADS and VDU: acquisition of data and writing (correction, improvement and editing); FC and FGM: interpretation of data and writing (correction, improvement and editing); MP: conceptualization, supervision and writing (original draft preparation). All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Ferdinando Antonio Gulino and Marco Palumbo are serving as the Editorial Board members of this journal. We declare that Ferdinando Antonio Gulino and Marco Palumbo had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Johannes Ott.

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