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The role of hysteroscopy in unexplained infertility

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Summary

Purpose of investigation: To evaluate pregnancy rate after diagnostic and operative hysteroscopy in nulliparous patients with infertility of unknown cause. *Materials and Methods:* The authors conducted this study on 92 nulliparous patients with unexplained infertility that underwent diagnostic hysteroscopy which showed an uterine lesion (submucous fibroids, uterine septa, polyps, synechias) and underwent operative hysteroscopy to remove the lesion between 2007 and 2011. Patients' data were retrospectively extrapolated from patient's charts, then the patients were called to ask if they had pregnancies after hysteroscopic surgery. *Results:* The present study showed a significant increase in pregnancy rate after hysteroscopic surgery (85% during the two years after the surgery). The most common endocavitary lesions were endometrial polyps (21%), uterine septa (25%), and submucous myomas (18%). *Conclusions:* According to the present data, hysteroscopic evaluation of nulliparous women with unexplained infertility could be useful to detect lesions not diagnosed with other tests, and the treatment of these endocavitary lesions plays an important role in the diagnostic and therapeutic iter. The results show a pregnancy rate of 85% in the patients treated for endocavitary lesions, but 15% of the patients, despite a normal uterine cavity, continue to have unexplained infertility and are classified as idiopathic infertility.

Key words: Hysteroscopy; Infertility; Intrauterine abnormalities; Idiopathic infertility.

Introduction

The term infertility, replacing the word "sterility", is indicated by the WHO (World Health Organization) as "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse", in the presence of regular menstrual cycles [1]; it is the complete inability to conceive because of an obstacle to fertilization, due to male and/or female factors [2, 3]. The human species is considered one of the less fertile of the planet [2], since the chance of conception is to just 25% in the fertile period. To this is added the fact that 5-10% of couples need 12-24 months to obtain a pregnancy [2].

The diagnostic evaluation of infertility is conducted on both partners: must be carried out in a fast and complete fashion, to lighten the psychological overload to which the couple is subjected. At the present time the causes of infertility are represented by 30% from male problems, 15% by ovulatory failure, 10% by tubal pathology, and 25% by disorders of the uterine cavity, 15% by idiopathic infertility, and 5% by rare problems [2].

The diagnostic iter for infertile couples consists of two levels of screening: a first level, to assess clinical history and physical examination, and a second level of exams to assess the cause of infertility.

According to WHO and European Society of Human Reproduction and Embryology, hysteroscopy plays a secondary role in this iter, after hysterosalpingography and pelvic ultrasound, despite its well known and studied advantages in the study of the uterine cavity: higher diagnostic sensitivity and specificity, low cost, absence of exposure to radiations, and the possibility to perform a biopsy of a diagnosed lesion in the same session of the diagnostic procedure.

Studies [4, 5] show that hysteroscopy can be a complementary procedure when anomalies are detected with hysterosalpingography and pelvic ultrasound, as hysteroscopy is the *gold standard* in the diagnosis of endocavitary uterine lesions in patients with infertility. The direct vision of the uterine cavity allows the immediate detection of morphologic and functional anomalies, which can interfere with embryonic implantation and growth, and enables the operator to intervene and recreate the normal uterine environment [6, 7]. In addition, hysteroscopy is considered a more accurate diagnostic tool, compared with the high rates of false negatives and false positives observed with hysterosalpingography relative to the assessment of the uterine cavity [8-10]: for this reason, many diagnostic protocols of patients with infertility include hysteroscopy [11, 12].

Recent reviews [13, 14] point out that there is an open debate regarding the role of hysteroscopic surgery in the management of female infertility; as a benefit with the hysteroscopy, removal of uterine lesions has been reported in observational studies, but more randomised studies are needed to validate this procedure in women with unexplained infertility or prior to assisted reproduction tech-

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nique (ART).

The aim of this study was to evaluate the impact of diagnostic and operative hysteroscopy in the uterine assessment of patients with unexplained infertility in terms of diagnosis of otherwise not detected lesions and pregnancy rate after removal of the possible cause of infertility.

Materials and Methods

This retrospective pilot study was conducted at "Sapienza" University of Rome, in the Hysteroscopy Unit of the Department of Gynecology-Obstetrics and Urological Sciences. The authors reviewed the clinical charts of infertile, nulliparous women that underwent diagnostic hysteroscopy between January 2007 and December 2011, and the patients with uterine endocavitary lesions also underwent operative hysteroscopy in the same years.

Inclusion criteria were: unexplained infertility, nulliparous, female partner aged 28-44 years, normal hormonal blood tests (FSH, LH, PRL, TSH, FT3, FT4), absence of endocrine dysfunctions in both partners, absence of uterine lesions in both pelvic ultrasound and hysterosalpingography, bilateral tubal patency, normal karyotype of both partners, vaginal swap negative for bacterial infection and Chlamydia, and absence of male factor of infertility.

From January 2007 to December 2011, 1,875 patients underwent diagnostic hysteroscopy, and 633 of these were infertile. Among the 633 infertile patients, 92 met the inclusion criteria. All the diagnostic and operative hysteroscopy were performed by the same surgeon. Diagnostic hysteroscopy was carried out with a 2.7 mm hysteroscope in vaginoscopy, with saline solution as a distention media with 50-60 mmHg pressure. The procedure was well tolerated and did not require analgesia in all cases. Operative hysteroscopy was performed with a ten-mm operative hysteroscope (resectoscope) with a solution of mannitol and sorbitol as distention media, under light sedation, and all removed lesions were sent to pathologic exam, which confirmed the diagnosis in all cases. Data were retrieved from clinical charts, then the selected patients were called to assess if they had pregnancies in the two years after surgery.

Results

Diagnostic and operative hysteroscopy were performed on 92 patients aged between 28 and 44 years (mean age 34). The authors obtained the following results: 18 patients (21%) had normal hysteroscopic findings and 74 patients (79%) showed an endocavitary uterine lesion (Table 1). The most common uterine lesions were endometrial polyps (21%), uterine septa (26%), and uterine fibroids (18%).

Among the studied patients in the two years following diagnostic/operative hysteroscopy, 78 had a pregnancy (85%): 16 of them had normal hysteroscopic findings (17%) and 62 had surgery for uterine pathology (68%). Fourteen patients did not achieve a pregnancy in the follow-up time (15%): two of them had a normal diagnostic hysteroscopy and 12 of them underwent operative hysteroscopy to remove the uterine pathology.

The authors divided the group of patients that underwent surgery in subgroups according to the removed uterine lesions and discovered that the pregnancy rate was different, as showed in Table 2.

Table 1. — *Diagnostic hysteroscopy results.*

	N	(%)
Normal uterine cavity	18	21%
Endometrial polyps	19	21%
Cervical polyps	10	11%
Uterine adhesions	4	4%
Submucous fibroids	17	18%
Uterine septa	24	26%

Table 2. — *Pregnancy rate after surgery, divided by type of uterine lesions.*

	Pregnant		Not pregnant	
Endometrial polyps	15	78%	4	22%
Cervical polyps	8	80%	2	20%
Uterine adhesions	4	100%	0	0%
Submucous fibroids	16	90%	1	10%
Uterine septa	19	79%	5	21%

Discussion

The assessment of the uterine cavity is one important step in the diagnostic iter of infertility. From this retrospective analysis emerged that in 79% of the cases of unexplained infertility, there was a missed diagnosis of an uterine lesion, despite the fact that every patient had a negative hysterosalpingography and pelvic ultrasound previous to diagnostic hysteroscopy: in these cases, hysteroscopy detected uterine lesions could be responsible for the infertility. The present authors report a rate of endometrial polyps (21%), submucous fibroids (18%), and uterine septa (25%), similar to the one reported in a recent study [15].

Regarding the pregnancy rate, the authors found that after the surgery for uterine submucous fibroids, uterine septa, and uterine polyps had respectively in 90%, 79%, and 78% of the cases a pregnancy, showing that the removal of lesions can interfere with the implantation of the embryo in the uterine cavity and can improve the pregnancy rate in this group of patients. The present findings are in line with the current literature [16-20], that shows that the pregnancy rate in patients with uterine submucous fibroids after removal improves significantly, demonstrating a role of the fibroids as a cause of infertility. The same results are obtained when the surgery is performed in patients with uterine polyps [21].

Regarding the correction of uterine septa, there are studies demonstrating the improvement of the pregnancy rate by 44-53% [22, 23], but there is still an open controversy, as most of the studies are conducted on patients with recurrent miscarriages and are not case-controlled studies, since they are performed with the same patients before and after surgery.

In this study, the authors did not collect data about the outcome of the pregnancy, because the heterogeneity of the lesions considered and the range of patients age did not allow simple conclusions about term pregnancy and miscarriage rate, and they reserve these data analysis to further studies.

The rate of patients which did not achieve a pregnancy (15%) is in line with the literature (10-16%), and these patients are classified with idiopathic infertility [2]. The incidence of idiopathic infertility should decrease if the diagnostic iter is improved, including new tests to identify all possible causes of infertility. For example, studies in women with abnormalities of certain proteins and genes (e.g. HOXA 10, HOXA 11, and Claudin-4) that could interfere with fertility are underway.

A study showed that the expression of the genes HOXA 10 and 11 in the endometrium could interfere with the implantation of the embryo and explain certain cases of idiopathic infertility [24]. Claudin 4 (CLDN-4) is a transmembrane protein, which was also observed in the endometrium. According to a study in 2013 [25], high levels of this protein may impair fertility.

Studies from Sharma *et al.* and Balakrishman *et al.* state that failure in obtaining a pregnancy, in the absence of disease, may depend on stress, as under stressful conditions progesterone turns into cortisol [26, 27], resulting in a decrease in the levels of progesterone in the body. At the same time, the prolactin level remains high because dopamine, the hormone of well being, decreases. The level of sex hormones thus lowers and this produces menstrual irregularities and anovulation. In humans, moreover, it would appear that exposure to certain endocrine disruptors (4-tert-octylphenol) would alter the functionality of sperm [28]. In the literature emerges that research on idiopathic infertility is still incomplete.

Conclusions

Infertility is, at this time, a condition that still leaves many interrogatives, and needs more validated scientific evidences. The use of standard guidelines is mandatory to identify a suitable diagnostic and therapeutic iter, to decrease the rate of idiopathic cases, and improve the pregnancy rate, and this can only be achieved with a multidisciplinary team work.

From the present study, the fundamental role played by hysteroscopy is clear in the diagnostic and therapeutic management of patients with otherwise unexplained infertility. Nevertheless, it is important to emphasize the need for new and improved diagnostic strategies to solve the problem of idiopathic infertility.

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