



Endometrial Pathology in Patients with Infertility: Experience at Fertility, Reproductive Medicine Center

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Abstract

Objective: To describe the prevalence of intrauterine pathology by hysteroscopy in infertile women treated at Fertilità.

Material and Method: Retrospective, observational, descriptive study of patients undergoing hysteroscopy between January 2020 and December 2022. Inclusion criteria: infertile women under 42 years of age with intrauterine pathology, who authorized hysteroscopy. Statistical analysis: GraphPad Prism 8.0.2 (GraphPad Software, Inc., San Diego, CA, USA). 95% CI for all proportions using the Wilson-Brown method. Fisher's exact test to compare proportions. The probability of pregnancy was calculated using Kaplan-Meier analysis. $P < 0.05$ was considered significant.

Results: Of 298 digital records, age, time and type of sterility were reviewed. Hysteroscopic findings in primary infertility: endometrial polyp, 78.1%; endometrial hyperplasia, 16.5%; endometritis, 3.3%; fibroids, endometrial Ca control before in vitro fertilization: 0.66% each. In secondary infertility: endometrial polyp, 71.4%; endometrial hyperplasia, 22.4%; myomatosis, insufficient sample, 1.36%. Endometrial Intraepithelial Neoplasia, acute endometritis, embryonic remains and longitudinal septum, 0.68%. 45.3% of the patients achieved pregnancy after hysteroscopy with some assisted reproductive technique.

Conclusions: In infertile patients with intrauterine pathology, the most frequent is endometrial polyposis. Other frequent pathologies are endometritis, hyperplasia and uterine fibroids. In clinical practice, imaging techniques will continue to be first-line tools for the study of the uterus and endometrium, but hysteroscopy is the gold standard for confirming the diagnosis and for its treatment.

Keywords: Hysteroscopy; Endometrial Polyp; Endometrial Hyperplasia; Endometritis; Myoma; Uterine Septum

Background

Infertility is a disease defined by the World Health Organization (WHO) as the impossibility of achieving a pregnancy after 1 year or more of having normal, regular sexual relations and without any method of family planning [1] or when the woman has had several abortions or preterm births that have not culminated in a live child. Infertility can be caused by disturbances in the male factor, the female factor, or both. In the female factor it can involve the cervical, uterine, tubal, pelvic or endocrine factor. Specifically, the uterine factor may be involved in anatomical aspects such as fibroids, endometrial polyps, Müllerian malformations, synechiae

[2,3] or functional aspects such as endometrial microbiota disorders [4,5].

Evaluation of the uterine cavity is often not considered necessary in the investigation of patients with infertility and normal menstrual cycles; however, intrauterine pathology can interfere with the implantation process and is not uncommon in women with infertility.

The morphological assessment of the myometrium and endometrium are fundamental in the study of patients with infertility,

since the alterations are not only associated with infertility, but can also be associated with repeated pregnancy loss or preterm delivery.

Diagnostic methods to assess uterine abnormalities include ultrasonography (US), hysterosonography (HS), hysterosalpingography (HSG), magnetic resonance imaging (MRI), laparoscopy, transvaginal hydrolaparoscopy or fertiloscopy [6,7] and hysteroscopy. Currently, hysteroscopy is used as an integral part of the evaluation of a couple with infertility, particularly for the diagnosis and treatment of intrauterine pathologies such as endometrial polyposis, uterine fibroids or synechiae [3].

Aim

The objective of this work was to describe the prevalence of intrauterine pathology diagnosed with hysteroscopy in women with infertility treated at Fertilità, a reproductive medicine center.

Material and Methods

A retrospective, observational, descriptive study of patients who underwent hysteroscopy as part of their infertility study at the Fertility reproductive medicine center between January 2020 and December 2022 was conducted.

298 patients who met the following inclusion criteria were included:

- Not older than 42 years of age (ranges: 20 to 42 years);
- Diagnosis of infertility, according to the WHO.
- Initial assessment of the complete infertile couple.
- Suspicion of intrauterine pathology by transvaginal ultrasound and/or hysterosonography and/or hysterosalpingography.
- Authorization to carry out the hysteroscopic procedure.

Patients who underwent hysteroscopy for reasons other than infertility such as intrauterine device removal or abnormal uterine bleeding were excluded.

Hysteroscopy was performed in the operating room, under sedation, in the 298 patients in the review. The hysteroscopy was scheduled between day 5 and 10 of the menstrual cycle. Patients were not prepared with contraceptives. Prophylactic intravenous antibiotic was administered in all cases. Hysteroscopy was performed with a 4-mm, 30° Karl Storz operating hysteroscope with

infusion pump for hysteroscopy with saline solution at 100-120 mmHg pressure. Cervical dilation with Hegar dilators was avoided whenever possible, although in some cases it was necessary. The procedure was considered complete as long as both ostium and all four walls of the uterine cavity could be observed. No resectoscope was used in any case, but only scissors and/or hysteroscopic forceps for biopsy. All tissue samples obtained were sent to pathology for a histopathological report.

The epidemiological data, findings and pathology reports were captured in the Fertilità reproductive medicine center database.

Statistical methodology

Data were stored in Microsoft Office Excel software (Microsoft Corporation, Redmond, WA, USA). Statistical analysis was performed with GraphPad Prism 8.0.2 (GraphPad Software, Inc., 2365 Northside Dr. Suite 560, San Diego, CA, USA). A 95% CI number was calculated for all proportions using the Wilson-Brown method. Fisher's exact test was used to compare proportions. The probability of pregnancy was calculated using Kaplan-Meier analysis. A $p < 0.05$ was considered significant.

Results

A total of 298 women met the inclusion criteria and were included in the review. The average age of the entire universe of included patients was 35.2 years and the average infertility time of the entire universe was 4.2 years. Of the total number of patients, 151 of them suffered from primary infertility (50.67%) and 147 suffered from secondary infertility (49.32%). The mean time to infertility in the primary infertility group was 4.4 years and in the secondary infertility group it was 4.0 years. See table 1.

Hysteroscopic findings

In the primary infertility group, there was preoperative suspicion of endometrial polyposis in 120 cases; at least one polyp was found in 118 cases, that is, 98.3% diagnostic certainty. This represented 78.1% of the cases in this group. The second most frequent pathology in this group was endometrial hyperplasia, with 25 cases; that is, 16.5% of the cases of this group. In third place was endometritis, with 5 cases; that is, 3.3% of the cases. A case of uterine fibroids that represented 0.66% of the cases. A control hysteroscopy was performed on a patient who would enter the assisted reproduction program due to a history of endometrial Ca. Another case was reported by pathology as "insufficient sample" (0.66% of the cases in this group). See table 2.

Type of sterility	Primary	Secondary
	151 (50.67%)	147 (49.32%)
Age (mean)	35.0 years old	35.5 years old
Time of sterility (mean)	4.4 years old	4.0 years old

Table 1: General characteristics of the 298 patients.

	PRIMARY infertility
Polip	118 (78.1%)
Hyperplasia	25 (16.5%)
Endometritis	5 (3.3%)
Uterine fibroid	1 (0.66%)
Ca	1 control for history of endometrial Cancer (0.66%)
Sample without pathology report (insufficient sample)	1 (0.66%)

Table 2: Pathology reports of the group of patients with PRIMARY infertility.

Of the 147 cases in the secondary infertility group, there was preoperative suspicion of endometrial polypsis in 110 cases and at least one polyp was found in 105 cases, that is, 95.4% diagnostic accuracy. This represented 71.4% of the cases in this group. The second most frequent pathology in this group was endometrial hyperplasia, with 33 cases; that is, 22.4% of the cases of this group. In third place was myomatosis, with 2 cases; that is, 1.36% of the cases. In one case (0.68%) they reported Endometrial Intraepithelial Neoplasia. Also in one case (0.68%) acute endometritis was reported and in another case (0.68%) “embryonic remains” were reported. In one case (0.68%), the treating physician decided not to take a sample and in two cases the pathology department reported “insufficient sample” (1.36% of the cases in this group). In one case (0.68%) the hysteroscopic finding was a longitudinal septum. See table 3.

Fertility results after operative hysteroscopy

A total of 135 (45.3%) of the 298 patients conceived a pregnancy after hysteroscopy, all with assisted reproductive techniques, either low or high complexity. No statistically significant differences were found between primary and secondary infertility in the pregnancy rate.

Discussion

The World Health Organization (WHO) recognizes infertility as a global public health problem, ranking it as the fifth largest serious disability in the young population [8].

	Secondary infertility
Polip	105 (71.4 %) 1 of them had protrusion into the cervical canal and external cervical orifice.
Hyperplasia	33 (22.44%)
Uterine fibroid	2 (1.36%)
Acute Endometritis	1 (0.68%)
endometrial intraepithelial neoplasia	1 (0.68%)
Does not take sample	1 (0.68%)
embryonic remains	1 (0.68%)
uterine septum	1 (0.68%)
Sample without pathology report (insufficient sample)	2 (1.36%)

Table 3: Pathology reports of the group of patients with SECONDARY infertility.

In our review, of the 298 women diagnosed with infertility, 50.67% had primary infertility and 49.32% had secondary infertility. Several studies around the world have shown that the incidence of primary infertility is higher than that of secondary infertility [8-11]. There are also reports that agree that in urban areas, like ours, the prevalence of primary infertility is higher than secondary [12]. In our statistics, the prevalence was practically the same. This is probably since it is a reproductive medicine center and patients are already pre-selected with suspicion of intrauterine pathology by a direct or indirect imaging study.

However, uterine lesions are common in patients with infertility and although the first line investigation tools for uterine factors are US (2D or 3D), HS and HSG, hysteroscopy is currently considered the standard of care. reference to evaluate the uterine cavity [3,13,14]; that is why different authors and associations in the world recommend its use as a basic tool in the diagnosis and treatment of the infertile couple [3,15,16].

Hysteroscopy has several advantages [7,17]:

- Confirms the diagnostic suspicion of anomalies detected by US, HS and/or HSG.
- Rule out intracavitary alterations in patients with infertility of unknown origin, according to the usual protocols.
- Confirms the anatomical and functional integrity, after repeated failures in assisted reproduction techniques.
- Establishes the causal diagnosis and surgical correction in the same surgical event 13; In fact, it can often provide definitive treatment for endocavitary lesions that could affect a woman’s fertility [18].

- It has a low risk of complications [19].

The available scientific evidence suggests that performing a routine hysteroscopy before the first attempt at highly complex assisted reproduction improves the clinical pregnancy rate; however, the live birth rate is not affected [20,21]; Due to the latter, we do not recommend hysteroscopy to all patients with infertility, but only to those in whom we justify its use due to the findings of the imaging studies (US, HS and/or HSG). This is the reason why in our review we found a very high percentage of correspondence between the preoperative and postoperative diagnoses (hysteroscopic findings and pathology report), particularly endometrial polyposis.

Endometrial polyposis

The most common intrauterine pathology diagnosed in our series of cases was endometrial polyposis (74.8% of the total; 78.1% in cases of primary infertility and 71.4% in cases of secondary infertility). This agrees with previous reports in our population [22], although the frequency found in our review is higher than that reported in other series, and this is because our review includes only pre-selected cases of patients whose indication for hysteroscopy was an intrauterine abnormality in the imaging studies. Endometrial polyps are the most frequently observed pathological finding in utero and are usually benign lesions [23]. Its precise frequency is not known, since up to just over 80% of cases may be asymptomatic [24]. On the other hand, in cases of abnormal uterine bleeding, up to 50% of cases involve polyps [25] and up to 35% of cases of infertility²⁶. In highly complex assisted reproduction programs, this pathology has also been reported as one of the endouterine disorders most commonly diagnosed by hysteroscopy [27].

The mechanism by which polyps negatively affect fertility is because they interfere with uterine receptivity and embryo implantation [28], which is why their hysteroscopic resection is highly recommended before any fertility treatment [29-31].

Hyperplasia

The frequency with which we find this pathology differs from that found in other publications, where its frequency is significantly lower^{32,14}. This can probably be explained by the selection of patients included in our review and/or that it is a transitional stage between endometritis and endometrial polyposis.

Endometritis

Another relatively frequent pathology in our review was endometritis. Some studies have shown that a group of patients with infertility present vascular changes at the endometrial level that are observed as stromal edema, diffuse areas of hyperemia, and even endometrial polyposis, to the extent that it has been hypothesized that the axis of the nutritional vessel of functional polyps may originate from the evolution of vascular changes associated with endometritis³³. Unfortunately, endometritis can be asymptomatic or with minimal changes in the menstrual pattern that, on some occa-

sions, do not attract the attention of the patient or the clinician. In addition, for its diagnosis by pathological anatomy, an experienced pathologist is required to be able to make the diagnosis correctly.

Uterine fibroids

It has been reported that fibroids contribute to infertility in 5-10% of cases and that as a single cause the frequency can be 1-2.4% [34]. In our review, the frequency in the primary infertility group was 0.66% and in the secondary infertility group it was 1.36%, which is consistent with what is reported in the available scientific literature. These percentages are largely explained by the diagnostic sensitivity and specificity of other tools such as transvaginal ultrasound for the accurate diagnosis of uterine fibroids and its location in the myometrium. Theories related to the mechanism by which they cause infertility are basically synthesized in uterine contractility dysfunction, myometrial and endometrial dysfunction, and distortion of the uterine anatomy and its cavity [35]. The relationship between fibroids and infertility is greater when there is an intracavitary component. In these cases, hysteroscopy not only helps to establish the diagnosis with reported sensitivity, specificity, and predictive values of almost 100% [36], but also surgical treatment by myomectomy in the same intervention. Thus, submucosal fibroids should also be removed in infertile patients, regardless of the size of the fibroid or the presence of symptoms other than infertility [19,37,38]. For submucosal fibroids types 0, 1, and 2 [39], hysteroscopic myomectomy is the standard approach; pregnancy rates after myomectomy range from 16 to 77%, with a median value of 45% [40].

Müllerian malformations

A very infrequent finding in our review was the uterine septum, which, although it is not properly considered a primary factor of infertility, up to 40% of the patients who have it may present infertility, increased risk of repeated pregnancy loss or complications. Obstetrics [41]. The prevalence of the uterine septum in infertile women varies, but it is estimated to be almost four times higher than in our review [42]. Hysteroscopic resection of the uterine septum is performed worldwide to improve reproductive outcomes. Several studies have reported an increase in pregnancy rates after metroplasty, ranging from 23% to 80% [43].

Conclusions

The report of our review has the limitation that the patients included in it are patients with a diagnosis of infertility and this can be due to a single factor, or more than one factor involved in the case, such as, for example, male, endocrine, tubal, etc.

Endometrial polyps were the most common uterine abnormality found in both the group of women with primary and secondary infertility. Other pathologies that we found were endometritis, hyperplasia, and uterine fibroids and this is consistent with the intracavitary pathology that commonly affects fertility [44].

In our study, the pregnancy rate after polypectomy is 43.5%, which is slightly lower compared to other studies, where it is between 50 - 78.3% [30,31]. And although the evidence that performing a polypectomy improves low or high complexity clinical pregnancy rates is not strong [45], in our experience it is better to perform it before any infertility treatment.

In reviewing our experience, due to the number of cases of Müllerian malformations or uterine fibroids, we cannot reach definitive conclusions.

On the other hand, this review allows us to confirm a very good concordance between the preoperative diagnosis with US, HS and/or HSG and the postoperative diagnosis: to a large extent this is due to the great advances in imaging equipment technology, particularly in transvaginal ultrasound equipment and the experience of our sonographers.

Hysteroscopy, due to its diagnostic and therapeutic potential, should be considered as an important tool in the gynecological armamentarium. And although in clinical practice direct and indirect imaging techniques will continue to be first-line tools in the study of the uterus and endometrium, hysteroscopy should be the reference standard to confirm the diagnosis and for its treatment.

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