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Clinical relevance of endometrial polyps diagnosed by hysteroscopy in 613 infertile women: a retrospective, single-center, cohort study

Abstract

Purpose: This study aimed to reveal the clinical significance of hysteroscopyin infertility treatment.

Methods: This retrospective, single-center, cohort study included 613 women of reproductive age who underwent hysteroscopy between April 2011 and March 2016. All women underwent a routine infertility work-up including transvaginal sonography, hysterosalpingography, and blood tests, and analysis of their husband's semen was performed. The Student t, Mann-Whitney, and Fisher exact tests were used to analyze the data.

Results: Hysteroscopy as a routine work-up revealed an abnormal uterine cavity in 141 women (22.1%) and 114 endometrial polyps (80.9%). Endometrial polyps were more frequently observed in those with primary infertility ($p<.005$) and endometriosis ($p<.005$) than those without these conditions. Endometrial polyps were rarely observed in those with recurrent pregnancy loss ($p<.05$).

Conclusion: Hysteroscopy is recommended as a routine work-up before fertility treatment given the prevalence of endometrial polyps, especially for women with endometrioma, and their impacts on embryo implantation failure.

Keywords: endometrial polyps, hysteroscopy, infertile women, gynecological procedure

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Abbreviations: NSAID, non-steroidal anti-inflammatory drug; TCR, trans-cervical resectoscope; ART, assisted reproductive technologies; IVF, in vitro fertilization; HSG, hysterosalpingography; VAS, visual analogue scale

Introduction

Abnormal intrauterine findings are accompanied with embryo implantation failure. As 57% of infertile women have abnormal findings in their uterine cavities,[1] it should be clinically meaningful to investigate uterine cavities of infertile women. The uterine cavity can be visualized by hysteroscopy without anesthesia; thus, hysteroscopy is more suitable for uterine cavity exploration than transvaginal ultrasonography and hysterosalpingography.[1] and it can be performed as a reliable and safe office gynecological procedure.

An endometrial polyp is the most frequently encountered lesion in the infertile uterine cavity, and recent systematic reviews and meta-analysis have shown that removal of endometrial polyps may increase the rates of pregnancy and live birth.[2,3] Nevertheless, it is uncertain how crucial the roles of endometrial polyps play in infertility and pregnancy loss, and there is no evidence about the role of hysteroscopy as a basic infertility evaluation tool.[4] Recently, more attention has been paid to shortening the time to pregnancy in the infertility work-up because of the dramatic increase in the average age of marriage and increase of older women with hopes of childbearing. Therefore, it should be noteworthy to clarify the clinical impact of hysteroscopy in the early phase of the infertility work-up, especially for women aged 35-45 years.

We have conducted hysteroscopy as a primary investigation for infertile women and those with recurrent pregnancy loss. In this study, the clinical relevance of hysteroscopic investigation of endometrial polyps as a routine work-up for new patients with hopes of childbearing was retrospectively assessed along with infertility factors by clarifying the characteristics of women with endometrial polyps.

Materials and methods

Study population

We screened 633 women who visited our hospital with hopes of childbearing for 5 years from April 2011 to March 2016. Hysteroscopy was performed with patients' informed consent in 613 cases (96.8%), excluding those in whom pregnancy was found or suspected at the first examination or those in whom hysteroscopy could not be performed because of severe cervical stenosis.

Hysteroscopy

The diagnostic hysteroscopies were performed using a 3.8mm sheath (Olympus Corporation, Tokyo, Japan). Patients underwent the examination during the first half of their menstrual cycle and were given non-steroidal anti-inflammatory drug (NSAID) suppositories 30 minutes before the examination if they preferred analgesia. The hysteroscope was inserted without cervical dilation. Distention of the uterine cavity was accomplished with normal saline. The procedure was performed by 15 physicians, and hysteroscopic findings were

recorded by creating a checklist. Antibiotics were administered to prevent infection.

Data collection

Couples completed a questionnaire about their pregnancy history, past history and duration of infertility at the first visit. All patients had undergone a routine infertility work-up including transvaginal sonography, hysterosalpingography, and blood tests, and analysis of their husband's semen was performed. The tubal factor was determined as bilateral tubal obstruction or perifimbrial adhesions on hysterosalpingography. Male sex factor included spermatogenic dysfunction according to World Health Organization criteria (1999) and sexual dysfunction identified in the questionnaire at their first visit. Ovulatory disorders included polycystic ovary syndrome and hypothalamic or pituitary disorders. Endometriosis was determined in those with ovarian endometrioma detected by transvaginal sonography. Recurrent pregnancy loss was determined in cases with repeated miscarriage at least twice.

Statistical analysis

Data are expressed as the mean±standard deviation for continuous variables. Differences between two groups of normally distributed variables were assessed using the Student t test, whereas non-normally distributed variables were evaluated with a non-parametric test (Mann-Whitney test) and Fisher exact test when the expected frequencies were small. A p value <.05 was considered significant.

Results

Hysteroscopy was performed in 613 women, with a mean age of 34.2±4.4 years and mean body mass index of 22.15±3.64 kg/m^2. The mean duration of infertility was 2.82±2.41 years. There were 440 (71.8%) and 173 (28.2%) cases of primary infertility and secondary infertility (including recurrent pregnancy loss), respectively.

Abnormal findings of the uterine cavity were observed in 141 of 613 cases (22.1%): 114 endometrial polyps (80.9%), 22 sub mucosal fibroids (15.6%), 3 uterine septa (2.1%), and 2 adhesions (1.4%) (Figure 1). All patients had no complications caused by hysteroscopy.

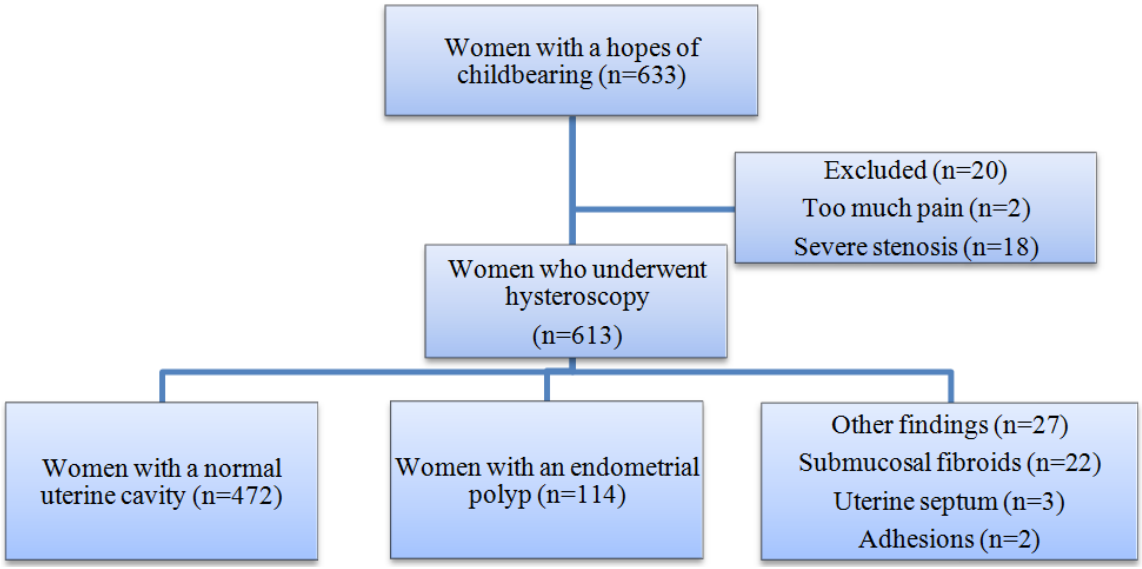

Figure 1 Hysteroscopic findings of 613 women of childbearing age.

Endometrial polyps were significantly frequent in patients with primary infertility than in those with secondary infertility (p<.05) (Table 1).

Table 1 Hysteroscopic findings according to type of infertility

	Primary, n (%)	Secondary, n (%)	
Normal uterine cavity	329 (74.8)	143 (82.7)	0.04
Abnormal uterine cavity			
Endometrial polyps	96 (21.8)	18 (10.4)	0.008
Submucosal fibroids	12 (2.7)	10 (5.7)	ns
Uterine septum	2 (0.5)	1 (0.6)	ns
Adhesions	1 (0.2)	1 (0.6)	ns
Total	440	173	

In the endometrial polyp group (n=114), the age-specific prevalence rate was highest at age 35-39 years (p<.05) (Table 2). We also compared the relationship with infertility factors (including recurrent pregnancy loss) and normal uterine cavity (n=472). Endometrial polyp was frequently accompanied with endometriosis (p<.005) and rarely with recurrent pregnancy loss (p<.05) (Table 3).

Table 2 Women with endometrial polyps according to age group

Age (y)	Polyps/women, n (%)
≤29	15/100 (15.0)
30-34	33/202 (16.3)
35-39	54/234 (23.1)
≥40	12/77 (15.6)
Total	114/613

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Table 3 Comparison of women with polyps and normal findings

	Women with polyps (n=114)	Women with normal findings (n=472)	P value
Age(y)	34.6±4.3	34.0±4.62	ns
<35 years	48	245	
≥35years	66	227	ns
BMI (kg/m^2)	22.74±5.08	22.00±3.62	ns
<25	92	385	
≥25	22	87	ns
Duration of infertility (y)	3.10±2.39	2.57±2.22	ns
Type of infertility, n(%)			
Primary	96 (84.2)	329 (69.6)	
Secondary	18 (15.8)	143 (30.4)	0.0015
Causes for infertility			
Unexplained	57	232	ns
Tubal factor	25	85	ns
Ovulatory disorder	8	68	ns
Male sex factor	8	43	ns
Endometriosis	15	18	0.0013
Recurrent pregnancy loss	1	26	0.0419

BMI, body mass index; ns, not significant

Among 114 cases that had endometrial polyps, 21 cases underwent polypectomy at the secondary hysteroscopic procedure using transcervical resectoscope (TCR), and 6 cases (28.6%) got pregnant within 1 year after polypectomy. Five out of these 6 cases got pregnant without advanced assisted reproductive technologies (ART), while 21 out of 93 unresected cases got pregnant without ART.

Discussion

Hysteroscopy is frequently conducted for evaluation of the uterine cavity,[5] and an endometrial polyp is a common lesion found during hysteroscopy. In the present study, 18.6% of new patients with hopes of childbearing had endometrial polyps. In previous studies, endometrial polyps were observed in 8.3% of patients before assisted reproductive technology (ART)[6] and 32% of patients undergoing in vitro fertilization (IVF).[7] In these studies, hysteroscopy was performed as a routine investigation before starting ART. Additionally, there are other studies in which endometrial polyps were found in 24% of infertile women[8] and even in only 5.8% of asymptomatic patients undergoing IVF.[9] Nevertheless, there should be a general concern for the invasiveness of hysteroscopy as a routine investigation, which is why the present study was conducted.

NSAID suppositories were used before the procedure according to the patient's request. Receiving tramadol or celecoxib orally at 1 hour before hysteroscopy has been reported to effectively reduce pain during and even 30 minutes after the procedure.[10] In our study, 0.3% of women could not undergo hysteroscopy because of severe pain even with this premedication, and another 2.8% of them could not undergo hysteroscopy because of cervical stenosis. It must be kept in mind that the hysteroscope will not be able to be inserted in some patients. Transvaginal sonography is a minimally invasive examination that has excellent sensitivity and specificity in detecting intrauterine abnormality,[11] but its efficacy is relatively poor compared with hysteroscopy in terms of accurately determining the location of polyps. As the location of an endometrial polyp may affect spontaneous pregnancy rates and fertility outcome,[12] hysteroscopy would offer a significant advantage over indirect methods by providing direct view of the uterine cavity. In this study, six out of 21 cases (28.6%) got pregnant within 1 year after TCR. But the frequency how many infertile cases bear unexpected polyps was unfortunately obscure, and as the nature of retrospective surveillances, the clinical decision to conduct TCR was made under the usual outpatient consultation, resulting in that the clinical benefit of TCR after routine hysteroscopy on conception was never clarified with our results. Nevertheless, to some extent clinical efficacy of polypectomy cannot be dismissible for infertile females due to the low cost not accounting for ART fees as well as prompt conception. A retrospective metanalysis also indicates an enough clinical benefit of polypectomy on an increased rate of clinical pregnancy for patients underwent intrauterine insemination (Z-score 5.94, $p<0.00001$), but not in vitro fertilization/intracytoplasmic sperm injection cycles (Z-score 1.43, $p=0.15$).[13] Furthermore, concerning the background that more than 40% of patients who undergo hysterosalpingography (HSG) experience severe pains with the Visual Analogue Scale (VAS)≥6.0 and 3.5% of them experience intolerable pains with VAS≥8.0,[14] hysteroscopic observation would be a reasonable alternative in outpatient clinic.

It is not well understood why endometrial polyps are associated with infertility. Some of the reasons may be mechanical interference with

sperm transport, embryo implantation, and intrauterine inflammation or increased production of implantation-inhibitory factors such as glycodelin.[15] As a mechanical problem, an endometrial polyp can cause hypermenorrhea and dysmenorrhea, but an endometrial polyp is found in only 10% of women with eumenorrhea[16] and15.6% of infertile women without menstrual abnormalities.[8] In the present study, endometrial polyps were observed in 18.2% of women with hopes of childbearing, but most patients were also asymptomatic menstrual cycles. Moreover, the prevalence of an endometrial polyp was especially higher in women aged 35-39 years than in those of other ages ($p<.05$). Thus, a hysteroscopic investigation might be considered useful in older infertile women, even in those without remarkable menstrual abnormalities.

Another infertile factor caused by an endometrial polyp may be endometriosis. Herein, the prevalence of endometrial polyps was significantly increased in women with endometriotic cysts ($p<.005$). It has been also reported that endometrial polyps were observed in 46.7% of infertile women with endometriosis.[17] Both an endometrial polyp and endometriosis have common pathophysiology of estrogen-dependency and active angiogenesis. Endometriosis is associated with endometrial flow reflux, and an endometrial polyp may exacerbate the reflux, causing an obstacle. As it is difficult to detect all endometriosis by ultrasonography, minimal or mild endometriosis without endometrioma might have been overlooked in our study. Although this is within a speculation and further investigation should be warranted, it is still considerable that a certain proportion of cases classified as unexplained infertility have endometrial polyps with minor endometriosis caused by endometrial reflux. If diagnostic laparoscopy would have been also performed in our study, the number of women diagnosed with endometriosis may have increased.

An endometrial polyp was less frequently observed among patients with a history of recurrent pregnancy loss in the present study ($p<.05$), and the low occurrence rate is compatible with that in previous studies reporting rates as low as 0.6%~5%.[18,19] Compared with congenital uterine morphological deformities which are infamous to be associated with recurrent pregnancy loss, endometrial polyp may not have so much impact on recurrent pregnancy loss after embryo implantation probably because it may cause more disorders in embryo implantation by chronic intrauterine inflammation and do more harm in tuboovarian route with endometrial reflux. Regarding the high-frequency of endometrial polyp and its clinical impact on infertility, to detect unexpected small endometrial polyps under the direct view of hysteroscopy should be designated more clinically important than to evaluate uterine morphology by HSG or transvaginal sonohysterography with indirect view.

Conclusion

In this cohort study, 96.8% of women with hopes of childbearing were able to undergo hysteroscopy without anesthesia, and 22.1% of them had abnormal findings in their uterine cavities, of which 80.9% also had endometrial polyps. In addition, the prevalence of an endometrial polyp was significantly higher in older women with primary infertility than in those with endometrioma, but low in those with recurrent pregnancy loss. There is a limitation in statistical power as the nature of a retrospective, single-center, cohort study, but still given the high prevalence of an endometrial polyp and its adverse effect on implantation failure, hysteroscopic investigation and intervention are recommended before starting ART.

Data availability

The data used to support the findings of this study are available from the corresponding authors upon request.

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Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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