Detection of intracavitary lesions in 820 infertile women: comparison of outpatient hysteroscopy with histopathological examination

Diagnostyka patologii wewnątrzmacicznych u 820 niepłodnych pacjentek – porównanie ambulatoryjnej histeroskopii z badaniem histopatologicznym

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Abstract

Objectives: *The aim of the study was to compare the results of a diagnostic hysteroscopy with a histopathology examination (referential test) in a group of infertile women.*

Materials and methods: *Eight hundred and twenty infertile patients were included in the study. The subjects with intracavitary lesions underwent operative hysteroscopy to enable the removal of polyps and intracavitary myomas. Endometrial biopsy was performed in all patients with no pathologies in hysteroscopy. The removed tissue underwent histopathological examination.*

Results: *The mean age was 32.9 ± 4.1. A total of 648 (79%) patients were diagnosed with primary and 172 (21%) with secondary infertility; 542 (66.1%) hysteroscopies were performed with no anesthesia and 278 (33.9%) hysteroscopies were performed in short total intravenous anesthesia. Sensitivity and specificity, accuracy, error, positive predictive value (PPV) and negative predictive value (NPV) of hysteroscopy in detecting endometrial lesions were 99.6%, 96.6%, 97.4%, 2.6%, 92.2% (PPV) and 99.8% (NPV), respectively. The agreement between hysteroscopy and pathology report was very high (kappa K=0.94). In case of normal uterine cavity, 562 of the 563 endometrial samples showed evidence of normal endometrium. In all 32 cases of resected submucosal myomas histopathology confirmed the hysteroscopic findings (sensitivity100%, specificity 100%, accuracy 100%, error 0%, kappa K=1.0). Both, hysteroscopy and histopathology confirmed the presence of endometrial polyps in 199 cases. The diagnosis of a polyp was not confirmed in histopathological findings (false-positive results) in 20 hysteroscopies. No endometrial polyps were missed during hysteroscopy. Sensitivity, specificity, accuracy, error, positive and negative predictive values in detecting endometrial polyps were 100%, 96.8%, 97.6%, 2.4%, 90.9% (PPV) and 100% (NPV), respectively. The Kappa coefficient agreement between hysteroscopy and histopathology for endometrial polyps was 0.91.*

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Conclusions: *Hysteroscopy is a method of high sensitivity and specificity in detecting pathologies, but in case of a pathology it cannot replace histological examination. Our result show that a routine endometrial biopsy performed in infertile patients with no pathology in hysteroscopy should not be recommended.*

Key words: **hysteroscopy** / **accuracy** / **infertility** / **histopatology** / **uterus** / / **endometrial polyp** /

Streszczenie

Cel pracy: *Celem pracy było porównanie diagnozy histeroskopowej z wynikiem badania histopatologicznego (badanie referencyjne) w grupie niepłodnych pacjentek.*

Materiał i Metody: *Do badania zakwalifikowano 820 niepłodnych pacjentek. Pacjentki z rozpoznaną nieprawidłowościami zostały poddane operacyjnej histeroskopii podczas której usunięto zdiagnozowane polipy i mięśniaki. Pacjentki u których nie stwierdzono patologii podczas histeroskopii miały wykonaną biopsję endometrium. Usuniętą tkankę przesyłano, do badania histopatologicznego.*

Wyniki: *Średni wiek pacjentki wynosił 32,9±4,1. U 648 (79%) pacjentek stwierdzono niepłodność pierwotną , a u 172 pacjentek (21%) niepłodność wtórną. 542 histeroskopii (66,1%) przeprowadzono bez znieczulenia zaś 278 (33,9%) histeroskopii wykonano w krótkim znieczuleniu ogólnym dożylnym. Czułość, swoistość, trafność, błąd dodatnia wartość predykcyjna (PPV), ujemna wartość predykcyjna (NPV) histeroskopii w wykrywaniu patologii wewnątrzmacicznych wynosiły odpowiednio: 99,6%, 96,6%, 97,4%, 2,6%, 92,2% (PPV) i 99,8% (NPV). Współczynnik zgodności histeroskopii i badania histopatologicznego był bardzo wysoki (kappa K=0.94). W przypadku pacjentek, u których obraz endometrium w badaniu histeroskopowym był prawidłowy, badanie histopatologiczne potwierdziło brak patologii u 562 z 563 badanych kobiet. We wszystkich 32 przypadkach resekcji mięśniaka histopatologia potwierdziła zmianę usuniętą w trakcie histeroskopii (czułość, swoistość, trafność 100%). U 199 pacjentek histeroskopia i badanie histopatologiczne potwierdziły obecność polipa endometrialnego. Podczas 20 histeroskopii zdiagnozowany polip nie został potwierdzony w badaniu histopatologicznym (wyniki fałszywie dodatnie). Czułość, swoistość, trafność, błąd dodatnia wartość predykcyjna (PPV), ujemna wartość predykcyjna (NPV) histeroskopii w wykrywaniu polipów endometrialnych wyniosły odpowiednio: 100%. 96,8%, 97,6%, 2,4%, 90,9% (PPV) i 100% (NPV). Współczynnik zgodności histeroskopii i badania histopatologicznego był bardzo wysoki : (kappa K=0.94).*

Wnioski: *Histeroskopia jest metodą o wysokiej czułości i swoistości w wykrywaniu patologii w obrębie jamy macicy, aczkolwiek w przypadku rozpoznania patologii nie może zastąpić badania histopatologicznego. Rutynowe pobieranie wycinków endometrium podczas histeroskopii u niepłodnych pacjentek z prawidłowym obrazem jamy macicy nie powinno być zalecane.*

Słowa kluczowe: **histeroskopia** / **dokładność** / **niepłodność** / **badanie histopatologiczne** / / **macica** / **polip endometrialny** /

Introduction

The uterus plays an essential role in reproduction. It is the place where spermatozoa are transported, get prepared to fertilization, and then the embryo is implanted and the fetus develops. The so called 'uterine factor' might be a cause of reproduction problems in 3-10% of women with fertility disorders [1-4].

That factor includes some congenital and acquired pathologies of the uterus, which can disturb spermatozoon migration, implantation and may lead to miscarriage and obstetrical problems [2, 5]. Hysteroscopic surgery performed to correct the uterine septum, intrauterine synechiae, and myomas that distort the uterine cavity, may be beneficial. Thus, it should be recommended to women with infertility or recurrent pregnancy loss.

Hysteroscopy is considered the 'gold standard' which makes lesions visible and allows for their removal [6]. It is possible to perform safe hysteroscopy within a short period of time with the use of modern endoscopes. Owing to small-diameter instruments, a specialist does not have to dilate the cervix and apply general anesthesia to perform the treatment [7]. Hysteroscopy is more effective in assessing uterine pathology and removal of polyps than blind techniques such as D&C [8, 9]. The use of blind biopsy or curettage in diagnosis and removal of benign pathologies in infertile women is believed to be of poor effectiveness and thus, should not be proceeded [10, 11]. Hysteroscopy offers a view of the cervical canal, uterine cavity and tubal ostia, the shape and the size of the uterus, the endometrium surface and intrauterine lesions. Direct visualization of the uterine cavity is possible with HS, but it provides no information about the myometrium or the adnexa, and only limited information about tubal patency [7,12] .

Numerous studies have shown that hysteroscopy may enable detection of focal lesions of the endometrial lining, missed by D&C alone. Therefore, in women who are at risk for endometrial hyperplasia and endometrial cancer, both the procedures or at least targeted biopsy should be performed. However, studies comparing hysteroscopy to histopathological findings in infertile women are scarce.

The aim of the study was to compare hysteroscopic findings in detecting endometrial lesions with pathological examination of the removed tissue.

Materials and Methods

Patients

Eight hundred and twenty infertile patients were included in the study. They underwent hysteroscopy during diagnostic evaluation for infertility in the *Gameta* Fertility Clinic, Łódź between 2007-2010.

Methods

Hysteroscopy was carried out between day 6 and 9 of the menstruation cycle, in an operating theatre with the use of the following endoscopic instruments: Bettocchhi Karl-Storz 4 mm hysteroscope, Aeskulap 1028 AR 7,0 mm resectoscope, Aesculap source of light Aesculap Axel 180. In order to obtain a panoramic view, 0.9% NaCl or 5% mannitol were used. After reaching the pressure of 70-100 mmHg and obtaining the panoramic view of the uterine cavity and tubal outlets, we evaluated the cervical canal of the uterus, the shape and the size of the uterine cave, the endometrium surface (folds, lumps, protrusions, hyperplasia, vessel arrangement), and intrauterine lesions. The diagnosed polyps, no bigger than 0,5 cm, were removed during the procedure with a 4 mm hysteroscope. More extensive lesions were removed with a resectoscope. The removed tissue underwent pathological analysis.

Statistical evaluation

While analyzing the hysteroscopic diagnosis, we adopted the pathological analysis as the referential test. Sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV) were calculated for hysteroscopy.

The Kappa coefficient confirming the agreement of the results was calculated with the use of the following formula:

$$K = 2 \times \frac{a \times b - b \times c}{[(a+c) \times (c+d) + (c+d) + (a+b) \times (b+d)]}$$

a – true-positive results of hysteroscopy
b – false-positive results of hysteroscopy
c – false-negative results of hysteroscopy
d – true-negative results of hysteroscopy

The following statistical values were adopted for the purposes of the current analysis: K<0.1 lack of agreement, K=0.11-0.40 low agreement, K=0.40-0.60 medium agreement, K=0.61-0.80 high agreement, K=0.81-1.00 very high agreement.

Results

All patients deemed eligible for hysteroscopy were of reproductive age. The mean age was 32.9±4,1. The majority of patients were at the age of 25-31 (38%). Only 15 patients were over 40 (1,8%). Six hundred and forty eight patients (79%) were diagnosed with primary and 172 patients (21%) with secondary infertility. Most patients did not report any symptoms (n=312; 38%) (Table I). The symptomatic patients reported: dysmenorrhea (n=188; 22.9%), irregular menorrhea (n=184; 22.4%), hypomenorrhea (n=70; 8.5%), hypermenorrhea (n=66; 8.0%). No concomitant complications were noted. Five hundred and forty two hysteroscopies (66%) were performed with no anesthesia and 278 in short total intravenous anesthesia (Table II).

In 237 cases, histopathology confirmed the pathology diagnosed by hysteroscopy. In 20 hysteroscopies the false positive results were caused by hysteroscopic recognition of the endometrial polyp, which was not confirmed by the following pathological examination. In the case of normal endometrial appearance during hysteroscopy, the subsequent pathology test confirmed the result of hysteroscopy in 562 patients. However, in 1 patient (1/563) diagnosed with normal endometrium the pathological examination showed endometrial hyperplasia without atypia (false-negative result). The patient was followed-up for the next 12 months and underwent two hysteroscopies combined with pathological examinations, which however, did not reveal any pathology. Sensitivity and specificity of hysteroscopy in detecting endometrial lesions were 99.6% and 96.6%, respectively. The accuracy and error were 97.4% and 2.6%. Positive and negative predictive values were 92.2% (PPV) and 99.8% (NPV), respectively. The agreement between hysteroscopy and pathologic exam was very high (K=0.94). Table III.

In all 32 cases, histopathology confirmed the findings of submucosal myomas resected by hysteroscopy (sensitivity 100%, specificity 100%, accuracy 100%, error 0%, K=1.0).

As far as endometrial polyps were concerned, in 199 cases both, hysteroscopy and histopathology confirmed the occurrence of lesions. The hysteroscopic diagnosis of a polyp was not confirmed by histopathology (false-positive results) in 20 cases. No endometrial polyp was missed during hysteroscopy. Sensitivity and specificity of hysteroscopy in detecting endometrial polyps were 100% and 96.8%, respectively. The accuracy and error were 97.6 % and 2.4%, respectively. Positive and negative predictive values were 90.9% (PPV) and 100% (NPV). The agreement between hysteroscopy and histopathology in detecting endometrial polyp was very high (K=0,94), (Table IV).

Table I. Patient characteristics.

	N	%
Age (mean + SD)	32.9 ± 4.1	
Infertility		
primary	648	**79**
secondary	172	**21**
Symptoms		
none	312	**38**
dysmenorrhea	188	**22.9**
irregular menorrhea	184	**22.4**
hypomenorrhea	70	**8.5**
hypermenorrhea	66	**8.0**

Table II. Anesthesia before hysteroscopy.

Hysteroscopy	Anesthesia	Non-anesthesia
Diagnostic	101 (12.3%)	468 (57.1%)
Polypectomy	145(17.7%)	74 (9%)
Myomectomy	32 (3.9%)	0
Total	**278 (33.9%)**	**542 (66.1%)**

Table III. Comparison of hysteroscopy with histopathological examination (referential method).

n=820	Histopathology	
Hysteroscopy	**yes**	**no**
Yes	237	20
No	1	562
Sensitivity	99.6	
Specificity	96.6	
Accuracy %	97.4	
Error %	2.6	
PPV %	92.2	
NPV %	99.8	
kappa (K)	0.94	

Table IV. Comparison of hysteroscopic diagnosis of endometrial polyps with histopathological findings.

n=820	Histopathology	
Hysteroscopy	**yes**	**no**
Yes	199	20
No	0	601
Sensitivity	100	
Specificity	96,8	
Accuracy %	97,6	
Error %	2,4	
PPV %	90,9	
NPV %	100	
kappa (K)	0,94	

Discussion

Uterine cavity abnormalities are commonly encountered in infertile population, therefore an accurate, cost-effective and safe method for evaluation and treatment of infertile patients is needed. Hysteroscopy can be performed successfully in an outpatient facility [7]. Application of thin endoscopes with mini-instruments allows the lesions to be successfully removed. Modern endoscopes enable to perform safe hysteroscopy within a short period of time. Owing to small diameter instruments, there is no need to dilate the cervix and to apply general anesthesia to perform the procedure. The treatment is safe and well-tolerated by patients [7]. Hysteroscopy provides a direct visualization of the endometrial cavity, thereby allowing targeted biopsy or excision of lesions identified during the procedure. At the same time, it is possible to remove the lesion and send it for analysis. Despite the fact that the procedure requires certain skills, hysteroscopy in most circumstances can be successfully performed at a gynecological office.

Office hysteroscopy in our study revealed an extremely high sensitivity, specificity and accuracy in the diagnosis of benign intracavitary lesions in 820 infertile patients. It also corresponded to pathological findings to a great extent. Hysteroscopy with endometrial sampling missed only one case of endometrial hyperplasia without atypia, which however, turned out not to be a prolonged pathology on further examination. The patient was followed-up for the next 12 months. The second and final diagnostic hysteroscopy combined with a pathological exam did not reveal any signs of a pathology.

Hysteroscopy showed perfect accuracy in diagnosing submucosal myomas distorting the endometrial cavity. In all cases, histopathology confirmed all the submucosal myomas resected by hysteroscopy (sensitivity 100%, K=1.0). The hysteroscopic diagnosis of a polyp was not confirmed by histopathology in 20 cases. These false-positive results diagnosed by hysteroscopy could have been a protruding part or a fold of the endometrium. At times, during resectoscopic removal of the lesions, material could be washed away by medium dilating the uterine cavity. Regardless of the consistency, the problem refers to myomas to a lesser extent.

Hysteroscopy was reported to demonstrate sensitivity, specificity, negative predictive value and positive predictive value of 94.2% 88.8%, 96.3% and 83.1% respectively, in predicting normal or abnormal endometrial histopathology. The highest accuracy of hysteroscopy was observed in diagnosing endometrial polyps, whereas the worst result was observed in detecting hyperplasia [13]. Yantapant et al., examined 60 female endometrial polyp patients, whose mean age was 31-40 years. Their study showed that the values of sensitivity, specificity and accuracy for the diagnosis of endometrial polyps were 93,3%, 33,3% and 87,9%, respectively [14]. Angioni in his study demonstrated sensitivity of 100%, specificity of 97%, with accuracy of 91% of hysteroscopy in diagnosing endometrial polyps. With regard to submucous myomas, sensitivity and specificity values were 100% and 98%, respectively and with the accuracy value of 99%. The kappa coefficient of concordance for polyps and myomas was 0.82 for hysteroscopy [15]. Dueholm compared hysteroscopy with the results of histopathological examination and hysterectomy (the gold standard). The overall sensitivity and specificity was 84% and 88%.

In our study, the accuracy of hysteroscopy reached the highest level for submucosal myomas (100%) and was higher than in the case of polyps. Wang et al., also showed higher accuracy of hysteroscopy in diagnosing submucosal myomas than in endometrial polyps (81.3% vs. 68.4%) [16].

In a prospective study by Epstein et al., 105 women with postmenopausal bleeding and endometrium >5 mm underwent conventional ultrasound examination and saline contrast sonohysterography. Hysteroscopy turned out to be superior to both, saline contrast sonohysterography and conventional ultrasound with regard to discriminating between benign and malignant lesions (sensitivity 84%, 44%, and 60%; false-positive rate, 15%, 6% and 10%, respectively [17].

One thousand five hundred hysteroscopies were matched with histology to estimate the accuracy of hysteroscopy in predicting endometrial histopathology. Histology showed normal endometrium in 927 patients. Endometritis, polyps, hyperplasia, and malignancies were found in 21, 265, 185, and 102 patients, respectively. Hysteroscopy showed sensitivity, specificity, NPV and PPV of 94.2%, 88.8%, 96.3%, and 83.1%, respectively, in predicting normal or abnormal histopathology of the endometrium. The highest accuracy was observed for the diagnosis of endometrial polyps; sensitivity, specificity, NPV, and PPV values were 95.3%, 95.4%, 98.9%, and 81.7%, respectively. The worst result was observed for the diagnosis of hyperplasia, with respective values of 70%, 91.6%, 94.3%, and 60.6% [18].

Pasqualotto et al., analyzed the clinical value of hysteroscopy in 375 women. The main indications for hysteroscopy were postmenopausal bleeding (164 patients, 43.7%) and abnormal premenopausal uterine bleeding (211 patients, 56.3%). The major pathological disorders included endometrial polyps (172; 45.9%) and submucous myomas (105; 28%). The sensitivity and specificity were 100% and 99%, respectively [19].

Kelekci et al., in their prospective study compared the diagnostic accuracy of office hysteroscopy for detecting intracavitary abnormalities in women with or without abnormal uterine bleeding scheduled for hysterectomy. The sensitivity and specificity of the office hysteroscopy in detecting intracavitary abnormalities were 87.5% and 100%, respectively [20].

Conclusion

In conclusion, hysteroscopy is a method of high sensitivity and specificity for detecting uterine cavity pathologies. However, in case of a pathology, it cannot replace the histological examination. Our results demonstrate that a routine endometrial biopsy in infertile patients with no pathology in hysteroscopy should not be recommended.

Oświadczenie autorów:

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