

Hysteroscopic and Pathologic Evaluation of Chronic Endometritis in Patients with Unexplained Recurrent Spontaneous Abortion

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ABSTRACT

BACKGROUND AND OBJECTIVE: Chronic endometritis is one of the most specific, but not the most common causes of infertility, which reduces the amount of pregnancy and poor results of pregnancy, such as preterm labor and abortion. The aim of this study was to evaluate the role of chronic endometritis in recurrent spontaneous abortions (RSA) and to determine the bilateral relationship between the histological and pathological findings of this inflammation.

METHODS: A case controlled-prospective observational study was performed on one hundred women 20-35 years in the Fatemeh Zahra infertility center and Rohani hospital. Patient group include forty patients with unexplained RSA and control group include 60 women that underwent hysteroscopy due to vaginal bleeding or other causes except RSA. All of the women underwent endometrial biopsy and examined by pathologist for presence plasma cells in stroma.

FINDINGS: In all patients endometritis rate was 8%. Patients with RSA had a significantly higher incidence of CE both hysteroscopically (30% vs. 6.7%; $p < 0.005$) and pathologically (27.5% vs. 6.7%; $p < 0.005$). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of hysteroscopy in the diagnosis of CE were 93.3%, 97.6%, 87.5% and 98.8% respectively. Also the PPV and NPV of hysteroscopy, sensitivity, specificity in the diagnosis of endometrial polyp were 100%, 87.3%, 76.3% and 100% respectively.

CONCLUSION: Based on the results, there was a significant association between CE and unexplained RSA. Due to high sensitivity and acceptable specificity of hysteroscopy in diagnosis of CE and endometrial polyp, we recommended hysteroscopic evaluation of patients with unexplained RSA.

KEY WORDS: *Recurrent Abortion, Chronic Endometritis, Hysteroscopy.*

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Introduction

Chronic endometritis (CE) is a chronic endometrial inflammation, which is often the most specific, but most uncommon cause of infertility, which is mostly asymptomatic or associated with symptoms such as pelvic pain, uterine bleeding, dyspareunia and discharge, and also reduces the amount of pregnancy and poor results of pregnancy such as preterm labor and abortion (1-4). Several studies have shown that CE plays a significant role in the frequent failure of Implantation and abortion (1,5,6).

Hysteroscopy is the only definitive method for observing and examining the uterine cavity. Hysteroscopy with biopsy has a good predictor of the status of uterine inflammation which is in fact the best way to diagnose intrauterine anomalies (7). Histologically, the diagnosis of CE is based on finding penetrating plasma cells in endometrial biopsy. On the other hand, the diagnosis of CE in hysteroscopy involves stromal edema, spotted or diffused perforation, and in some cases endometrial micro-polyps (less than 1 mm in size) (8-16). Recent studies have shown that in women with spontaneous abortion, the evaluation of intrauterine inflammation in hysteroscopy can be helpful in treating patients (17, 18). The researchers found that these patients had a higher incidence of chronic endometritis both in hysteroscopy and in pathology (1). Some studies did not support this usefulness (19,20). Spontaneous recurrent abortions are defined as three or more abortions before the 20th week of gestation. Its etiology is often uncertain. It may be multifactorial and about 1% of couples are involved. For this reason, in most cases, the causes of abortion are unclear and may play a major role in the immunological impairment of pregnancy (1,6,21-26). Therefore, due to the lack of adequate studies on the role of chronic endometritis in spontaneous abortion, this study was conducted to determine the hysteroscopic value in the diagnosis of chronic endometritis and histological and hysteroscopic findings in patients with a history of recurrent abortions with unexplained cause.

Methods

This prospective case-control study was approved by the Ethics Committee of the Babol University of Medical Sciences, code MUBABOL.HRI.REC.1396.157 and was performed on 100 women (20-35 years old) in Fatemeh Al-Zahra and Ayatollah Rohani hospitals in Babol which were divided into two groups. The case group included 40 women with a history of unexplained

recurrent abortions and 60 control women who had vaginal bleeding or other causes except RSA (Recurrent Spontaneous Abortion) and infertility underwent hysteroscopy.

All causes of repeated abortions such as genetic, immunologic, endocrine, anatomical and infectious disorders were excluded in the case group. To achieve this goal, all patients had normal hysterosalpingography, normal chromosomal karyotype for parents, normal lupus anticoagulant test, normal anticardiolipin test, normal testosterone hormones test. In addition, in the control group, having at least two non-aborted pregnancies whose last delivery was at least one year before the study was necessary. All patients in the follicular phase (between 13-5 cycles) were subjected to hysteroscopy.

Under general anesthesia, after the external vaginal and external cervix was washed with iodine solution, the uterine cavity was first filled with 5% dextrose serum then the hysteroscopy was performed by a gynecologist using the hysteroscope model (olympus and diameter 8 mm and 30-degree angle A40211-A), which was made possible by optical fiber, was considered appropriate inside the uterus. First, the cervical canal and the uterus cavity and then the mucus of the uterus were evaluated. Diagnostic criteria for chronic endometritis (CE) are localized or diffuse endometrial bleeding symptoms and, in some cases, polyps less than 1 mm in the endometrium (8). For all endometrial biopsies, the samples were taken at the end and the specimens were cut to a smaller portion and fixed with 10% formalin solution and after stacking a paraffin block and three micron sections, staining was done with hematoxylin and eosin and was investigated by pathologist with a microscope. Histopathologic diagnosis of CE was on the basis of edema of stroma, increased superficial stroma density and infiltration of lymphocytes and plasma cells. In other words, the presence of plasma cells in the endometrial stroma was considered as chronic endometritis. If less than one plasma cell was observed at the highest visual power, it was indicative of the absence of CE. After collecting data, statistical analysis was performed using SPSS software version 18, Chi-square and T test and $p < 0.05$ was considered significant.

Results

In the hysteroscopy and pathology examinations, two variables of edema or endometrial inflammation and endometrial polyp were noted. The mean age of the

subjects in the case group (recurrent abortion) was 28.83 ± 3.81 and 32.83 ± 2.3 years in the case group ($p=0.000$). Dysmenorrhea was 25% (10 cases) in the case group and 33.3% (20 cases) in the control group, which was not statistically significant. Dyspareunia in case group was 32.5% (13 cases) and in control group was 45% (27 cases), which was not statistically significant (Table 1). Patients had a clear higher incidence of endometritis in hysteroscopy (30% vs 6.7%: $p<0.05$) and 31 cases in the control group had polyps (51.7%). Of the 40 patients, 12 had endometritis in the hysteroscopy (30%) and 11 patients with pathology (27.5%). In the control group, the reported polyps were 34 (56.6%) in the pathology. Polyps in the case group were 3 (7.5%) in the hysteroscopy and 5 (12.5%) in the pathology ($p<0.05$). In this study, sensitivity and specificity of hysteroscopy for edema or endometritis were 93.3% and 97.6%, respectively. Also, the positive and negative predictive value were 87.5% and 98.8%, respectively. In addition, sensitivity and specificity of hysteroscopy for determination of endometrial polyps were 76.3% and 100%, respectively, and its positive and negative predictive values were 100% and 87.3%, respectively.

Table 1. Comparison of variables and study outcomes in two groups

Group Variable	Case(n=40) N(%)	Control(n=60) N(%)	P-value
Age(year) (Mean $\pm$ SD)	28.8 $\pm$ 3.8	32.8 $\pm$ 2.3	0.000
Dysmenorrhea	10(25)	20(33.3)	235
Dyspareunia	13(5.32)	27(45)	149
Endometritis in hysteroscopy	12(30)	4(6.7)	0.000
Endometritis in pathology	11(27.5)	4(6.7)	0.000
Polyp in hysteroscopy	3(7.5)	31(51.7)	0.000
Polyp in pathology	5(12.5)	34(56.6)	0.000

Discussion

In this study, endometritis was 8% in all patients. The present study showed that the incidence of endometritis in patients with unexplained abortion was significantly higher than that in the control group with a history of abnormal bleeding (6.7% vs 27.5%) ($p<0.05$). 30% prevalence of endometritis was also observed in patients with unexplained abortion. A study by

Zolghadr et al. in line with our study showed that patients with a history of secondary spontaneous abortion had a higher prevalence of chronic endometritis in the pathology ($p<0.0001$, 83.9% vs 45.9%) and hysteroscopy ($p<0.0001$, 24.6% vs 58.1%) (1). But in our study, except for one case, hysteroscopic and pathologic findings were correlated.

The sensitivity, specificity, positive predictive value and negative predictive value of hysteroscopy for diagnosis of CE were 98.4%, 56.23%, 63.5%, and 82.97%, respectively. A large number of studies have shown that chronic endometritis may interfere with successful pregnancy outcomes. In the study of cicinelli et al., which was performed on 910 women under 45 years of age, the highest percentage of endometritis in infertile women (40.7%) was in the hysteroscopic view, but in premenopausal women with abnormal uterine bleeding (20.9%), endometritis was observed in approximately 30% of infertile women and 35% of patients with AUB in histology (27).

Sensitivity, specificity and positive predictive value of hysteroscopy of endometritis based on diagnosis of edema and hyperemia were 91.8%, 92.6%, 63.9% and 98.8%, respectively. The diagnostic accuracy was 92.7%. Sensitivity and specificity of the positive and negative predictive values of hysteroscopy based on edema, hyperemia and micro polyp were 55.4%, 99.9%, 98.4% and 94.5%, respectively, and the accuracy of the diagnosis was 93.3 %. Liquid hysteroscopy is not a valid method for chronic endometritis, but it is useful for micro polyps. When hysteroscopy is done for infertility and AUB, you should always seek for signs of endometritis (27).

Our findings showed that hysteroscopy has limitation for diagnose of endometritis in RSA patients. This finding suggests that hysteroscopy is not useful in endometritis screening in asymptomatic infertile women. Further studies are required to confirm the etiology of the endometritis in infertile women. These differences may be due to the choice of patients (20). In the study of Kitara, according to our findings, about 54 patients with recurrent abortions, 31 patients had unexplained abortions, 12.9% had endometritis in pathology and hysteroscopy, all were before 11 weeks (24). Because the findings for evidence of association between endometritis in RSA and recurrence of infertility are low. For this reason, hysteroscopy is assisted in these areas. Previous studies have shown that hysteroscopy has a significant negative predictive value in the diagnosis of endometritis. This means that a

negative hysteroscopy can rule out endometritis in a suspect. Hysteroscopy in comparison to endometrial biopsy cannot alone detect localized lesions and is a slightly invasive diagnostic procedure that is usually performed in the office with local anesthetic and it has a high sensitivity and specificity for the diagnosis of endometritis.

In addition, hysteroscopy also has weaknesses such as expensive and inaccessible everywhere (therapeutic use especially in developed countries), the probability of perforation of the uterus and getting anesthesia and intolerance from patients (35%), and the difference in the prevalence of endometritis and the difference between the climates prevalence of endometritis. Because of these limitations, it may not be applicable in some cases in the clinic. (1,5,8-23). In our study, the overall endometritis rate, especially in RSA, was high in both methods, and in most cases, the percentages were related to polyps in the control group. Cicinelli et al. among the total of 157 patients diagnosed with hysteroscopy of endometritis, 101 (63.9%) of chronic endometritis were confirmed in pathology, and 61 (38.6%) of patients with chronic endometritis had micro polyps in hysteroscopy (27). With all these reports, chronic endometritis can be considered as one of the underlying causes and pathogenesis in patients with

recurrent abortions, and in some studies for Implicit recurrence in IVF cycles(1,5,20,35). Recently, some studies have shown that chronic endometritis causes failure in the acceptance of good quality embryos in transmission (14,16). There are other studies to confirm this implantation impairment (16,36).

The results of our study indicate that this inflammation of the uterine environment plays an important role in both the implantation process and the survival of the embryo. Endometritis causes changes in perineal, stromal and vascular visibility in hysteroscopy. The uterine cavity panoramic hysteroscopy can detect unpredictable lesions. Due to the high correlation between chronic endometritis and recurrent spontaneous abortion with unspecified cause and high sensitivity and specificity of hysteroscopy in endometritis and endometrial polyp, it is recommended that hysteroscopy should be considered in patients with unexplained abortion, if possible.

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References

1. Zolghadri J, Momtahan M, Aminian K, Ghaffarpasand F, Tavana Z. The value of hysteroscopy in diagnosis of chronic endometritis in patients with unexplained recurrent spontaneous abortion. *Eur J Obstet Gynecol Reprod Biol.* 2011;155(2):217-20.
2. Kitaya K, Yasuo T, Tada Y, Hayashi T, Taguchi S, Funabiki M, et al. Current understanding of chronic endometritis. *Diagnos Histopathol.* 2013;19(7):231-7.
3. Kasius JC, Fatemi HM, Bourgain C, Sie-Go DM, Eijkemans RJ, Fauser BC, et al. The impact of chronic endometritis on reproductive outcome. *Fertil Steril.* 2011;96(6):1451-6.
4. Fatemi HM, Popovic-Todorovic B, Ameryckx L, Bourgain C, Fauser B, Devroey P. In vitro fertilization pregnancy in a patient with proven chronic endometritis. *Fertil Steril.* 2009;91(4):1293. e9-e11.
5. Johnston-MacAnanny EB, Hartnett J, Engmann LL, Nulsen JC, Sanders MM, Benadiva CA. Chronic endometritis is a frequent finding in women with recurrent implantation failure after in vitro fertilization. *Fertil Steril.* 2010;93(2):437-41.
6. Yang R, Du X, Wang Y, Song X, Yang Y, Qiao J. The hysteroscopy and histological diagnosis and treatment value of chronic endometritis in recurrent implantation failure patients. *Arch Gynecol Obstet.* 2014;289(6):1363-9.
7. Song D, Li TC, Zhang Y, Feng X, Xia E, Huang X, et al. Correlation between hysteroscopy findings and chronic endometritis. *Fertil Steril.* 2019;111(4):772-9.
8. El-Mazny A, Abou-Salem N, El-Sherbiny W, Saber W. Outpatient hysteroscopy: a routine investigation before assisted reproductive techniques? *Fertil Steril.* 2011;95(1):272-6.
9. Makrakis E, Hassiakos D, Stathis D, Vaxevanoglou T, Orfanoudaki E, Pantos K. Hysteroscopy in women with implantation failures after in vitro fertilization: findings and effect on subsequent pregnancy rates. *J Minim Invasive Gynecol.* 2009;16(2):181-7.
10. Taylor E, Gomel V. The uterus and fertility. *Fertil Steril.* 2008;89(1):1-16.
11. Di Spiezio Sardo A, Guida M, Bettocchi S, Nappi L, Sorrentino F, Bifulco G, et al. Role of hysteroscopy in evaluating chronic pelvic pain. *Fertil Steril.* 2008;90(4):1191-6.
12. Bettocchi S, Achilarré MT, Ceci O, Luigi S. Fertility-enhancing hysteroscopic surgery. *Semin Reprod Med.* 2011;29(2): 075-082.
13. Smit JG, Kasius JC, Eijkemans MJ, Koks CA, Van Golde R, Oosterhuis JG, et al. The inSIGHT study: costs and effects of routine hysteroscopy prior to a first IVF treatment cycle. A randomised controlled trial. *BMC Womens Health.* 2012;12(1):22.
14. Cakmak H, Taylor HS. Assessment of Uterine Receptivity. In: Nagy Z, Varghese A, Agarwal A, (editors). *Practical Manual of In Vitro Fertilization.* New York:Springer; 2012. p. 559-66.
15. Perez-Medina T, Rayward J. Hysteroscopy and Infertility. *Diagnostic and Operative Hysteroscopy.* Jaypee Brothers Medical Publishers; 2007.p. 51.
16. Makrakis E, Pantos K. The outcomes of hysteroscopy in women with implantation failures after in-vitro fertilization: findings and effect on subsequent pregnancy rates. *Curr Opin Obstet Gynecol.* 2010;22(4):339-43.
17. Park HJ, Kim YS, Yoon TK, Lee WS. Chronic endometritis and infertility. *Clin Exp Reprod Med.* 2016;43(4):185-92.
18. Cicinelli E, Mitola PC, Crupano FM, Tinelli R, Trojano G. Chronic endometritis. *Hysteroscopy: Springer;* 2018. p. 661-4.
19. Cravello L, Porcu G, d'Ercole C, Roger V, Blanc B. [Identification and treatment of endometritis]. *Contracept Fertil Sex.* 1997;25(7-8):585-6.
20. Polisseni F, Bambirra EA, Camargos AF. Detection of chronic endometritis by diagnostic hysteroscopy in asymptomatic infertile patients. *Gynecol Obstet Invest.* 2003;55(4):205-10.

21. Chattopadhyay S, Sengupta TRV. Gynaecology for Postgraduate and Practitioners. Elsevier India. 2007. p.187.
22. Rao K. Recurrent Pregnancy Loss-ECAB. India: Elsevier; 2009.
23. McQueen DB, Bernardi LA, Stephenson MD. Chronic endometritis in women with recurrent early pregnancy loss and/or fetal demise. *Fertil Steril*. 2014;101(4):1026-30.
24. Kitaya K. Prevalence of chronic endometritis in recurrent miscarriages. *Fertil Steril*. 2011;95(3):1156-8.
25. Pandey MK, Rani R, Agrawal S. An update in recurrent spontaneous abortion. *Arch Gynecol Obstet*. 2005; 272(2):95-108.
26. Brezina PR, Kutteh WH. Recurrent Early Pregnancy Loss. In: Falcone T, Hurd W. editors. *Clinical Reproductive Medicine and Surgery*. New York: Springer; 2013. p. 197-208.
27. Cicinelli E, Resta L, Nicoletti R, Tartagni M, Marinaccio M, Bulletti C, et al. Detection of chronic endometritis at fluid hysteroscopy. *J Minim Invasive Gynecol*. 2005;12(6):514-8.
28. Fatemi H, Kasius J, Timmermans A, Van Disseldorp J, Fauser B, Devroey P, et al. Prevalence of unsuspected uterine cavity abnormalities diagnosed by office hysteroscopy prior to in vitro fertilization. *Hum Reprod*. 2010;25(8):1959-65.
29. El-Toukhy T, Sunkara SK, Coomarasamy A, Grace J, Khalaf Y. Outpatient hysteroscopy and subsequent IVF cycle outcome: a systematic review and meta-analysis. *Reprod Biomed Online*. 2008;16(5):712-9.
30. Feghali J, Bakar J, Mayenga JM, Segard L, Hamou J, Driguez P, et al. [Systematic hysteroscopy prior to in vitro fertilization]. *Gynecol Obstet Fertil*. 2003;31(2):127-31.
31. Bozdag G, Aksan G, Esinler I, Yerali H. What is the role of office hysteroscopy in women with failed IVF cycles?. *Reprod Biomed Online*. 2008;17(3):410-5.
32. Lorusso F, Ceci O, Bettocchi S, Lamanna G, Costantino A, Serrati G, et al. Office hysteroscopy in an in vitro fertilization program. *Gynecol Endocrinol*. 2008;24(8):465-9.
33. Pundir J, El Toukhy T. Uterine cavity assessment prior to IVF. *Womens Health*. 2010;6(6):841-8.
34. Paavonen J, Aine R, Teisala K, Heinonen PK, Punnonen R. Comparison of endometrial biopsy and peritoneal fluid cytologic testing with laparoscopy in the diagnosis of acute pelvic inflammatory disease. *Am J Obstet Gynecol*. 1985;151(5):645-50.
35. Lamonica R, Hartnett J, Engmann L, Sanders M, Maier D, Benadiva C. Immunohistochemistry confirms the presence of chronic endometritis in patients with recurrent implantation failure. *Fertil Steril*. 2006;86(3):S280.
36. Biran G, Weissman A, Farhi J, Avinoah I, Shahmorow M, Levran D. Is chronic endometritis a causative factor for repeated implantation failure in IVF-ET?. *Fertil Steril*. 2004;82(2):S128.