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# Hysteroscopic Evaluation of Chronic Endometritis Incidence in Unexplained Infertile Women with Recurrent Implantation Failure: Six Years Experience

# Tekrarlayan İmplantasyon Başarısızlığı Olan Açıklanamayan İnfertilite Olgularında Kronik Endometrit Sıklığının Histeroskopik Olarak Değerlendirilmesi: Altı Yıllık Deneyim

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**ÖZ**

**Amaç**: Tekrarlayan implantasyon başarısızlığı (TİB) olan açıklanamayan infertilite olgularında histeroskopik kronik endometrit (KE) insidansının değerlendirilmesi.
**Araçlar ve Yöntem**: Bu kesitsel retrospektif çalışmaya, Ocak 2014-Ağustos 2020 tarihleri arasında hastanemizin tüp bebek kliniğine başvurmuş olan 529 katılımcı dahil edilmiştir. Katılımcıların yaşları 18-39 aralığında değişmektedir. Katılımcılar, TİB olan açıklanamayan infertil olguları (Grup:1; n:187) ve TİB olmayan açıklanamayan infertil olguları (Grup:2; n:342) olmak üzere iki gruba ayrılmıştır.
**Bulgular**: Kadınların ortalama yaşı 31.6 ±5.1 olup, katılımcılara ait ortalama vücut kitle indeksi (VKİ) 24.6 ±2.5 olarak hesaplanmıştır. Histeroskopik bulgular ise şu şekildedir: 14 katılımcıda (%2.6) kronik endometritis, 19 katılımcıda (%3.6) polip bulunurken, katılımcıların 496'sında (%93.8) patolojik bulguya rastlanmamıştır. İki grup arasında yaş, VKİ, AMH seviyesi, toplam gonadotropin dozu, stimülasyon süresi, kazanılan oosit sayısı, MII ve PN bakımından istatiksel olarak anlamlı farklılık bulunmadığı görülmüştür. Yine, iki grup arasında, infertilite tipi (p=0.09) ve sigara kullanımı (p=0.5) bakımından istatistiksel olarak anlamlı bir fark bulunmamaktadır. Ancak test sayısı bakımından iki grup arasında istatistiksel olarak anlamlı bir farklılık (p=0.000) tespit edilmiştir. Ayrıca, iki grup arasında KE (p=0.1) ve polip (p=0.8) bakımından istatistiksel olarak anlamlı farklılık bulunmamış olup, endometriyal patoloji varlığı bakımından iki grup arasında istatistiksel olarak anlamlı farklılık (p<0.001) söz konusudur.
**Sonuç**: Bu çalışma, TİB olan kadınların daha yüksek KE insidansına sahip olmadığını, fakat bu hasta gruplarında endometriyal patolojilerin sayısının arttığını ortaya koymuştur. Bundan dolayı, açıklanamayan infertilitesi olan TİB hastalarında histeroskopi işleminin yapılması gerekmektedir.

**Anahtar Kelimeler:** açıklanamayan infertilite; histerokopi; kronik endometritis; tekrarlayan implantasyon başarısızlığı

**ABSTRACT**

**Purpose**: To evaluate histeroscopically-proved chronic endometritis (CE) incidence in unexplained infertility cases with recurrent implantation failure (RIF).
**Materials and Methods:** This cross-sectional retrospective study was done on 529 participants who attended our hospital's infertility clinic from January 2014 to August 2020. The participants were at the age of 18-39 years. We divided the subjects into two groups, i.e., unexplained infertile patients with RIF (Group:1; n:187) and unexplained infertile patients without RIF (Group:2; n:342).
**Results**: The women had a mean age of 31.6 ±5.1 years. Hysteroscopic findings were as follows:14 (2.6%) had chronic endometritis, 19 (3.6%) had polyps, and 496 (93.8%) had no pathological findings. Age, BMI, AMH level, total dose of gonadotropin, duration of stimulation, number of retrieved oocytes, Metaphase II (MII), and Pronucleus (PN) showed no significant difference between the two groups. Also, infertility type (P=0.09) and smoking(P=0.5) were not statistically different between the two groups. In addition, the two groups showed no statistically significant difference in polyps (p=0.8) and CE (p=0.1), while the two groups showed a statistically significant difference in endometrial pathology (p<0.001).
**Conclusion:** In this study, it was shown that those with RIF did not show a higher incidence of CE, but endometrial pathologies were increased in this group of patients. So hysteroscopy should be done in RIF patients with unexplained infertility.

**Keywords**: chronic endometritis; hysteroscopy; recurrent implantation failure; unexplained infertility

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## INTRODUCTION

Endometrium undergoes cyclical changes every month as a unique tissue resulting in proliferation, menstruation, and decidualization influenced by ovarian steroids.[1] Sometimes, higher cell density of the stroma, infiltration of lymphocytes and plasma cells present in the endometrial stroma, stromal fibroblasts, asynchronous maturation of epithelial cells, and superficial mucosal oedema results in chronic endometritis (CE).[2] CE is referred to as a type of inflammation in which there are plasma cells persistently in endometrium stroma and usually has no symptoms or has negligible symptoms, such as leucorrhea, pelvic pain, abnormal uterine bleeding, and dyspareunia.[3] The oligosymptomatic or asymptomatic inflammation is also accompanied by vaginal discharge, lower abdominal pain, fever, and abnormal menstrual function,[4] mild gastro-intestinal discomfort and, recurrent cystitis.[5] Since it is difficult to establish a diagnosis with no invasive endometrial biopsy, it remains unclear whether CE is prevalent among women at reproductive age.[6] However, it was reported that the CE incidence rate ranged between 2.8 and 56.8% among infertile women.[7,8] There is an increasing body of evidence that endometriosis is commonly associated with CE, and they have unexplained recurrent pregnancy losses, infertility with ambiguous etiology, and recurrent implantation failures (RIF) after in vitro fertilization (IVF) treatments.[9,10] Regardless of advancements in IVF practice, RIF is still a challenge that must be solved. RIF means when women have had failed IVF attempts three times with high-quality embryos.[11] The possible reasons for RIF include advanced maternal age, smoking status of both parents, elevated body mass index, and stress levels. Immunological factors such as cytokine levels and the presence of specific autoantibodies should be examined, as well as any infectious organisms in the uterus leading to CE. Uterine pathologies, such as polyps and myomas, as well as congenital anatomical anomalies, should be ruled out. Sperm analysis, pre-implantation genetic screening and endometrial receptivity should be considered and evaluated, and IVF protocols should be tailored to patients.[11] Those with recurrent pregnancy loss (RPL) and RIF had a higher incidence rate of CE, i.e., 9.3–67.6%,[9,12] and 14–67.5%,[13,15] respectively. These findings show a correlation between CE and RIF, which even displays a causal relationship with RPL. Although there have been recent innovations in reproductive immunology, testing techniques, stimulation protocols, and embryo culture, implantation continues to be one of the main factors limiting IVF success. Implantation is performed through several stages, including embryo apposition, adhesion, penetration, endometrial decidualization, and trophoblast invasion. Immune cells and cytokines tightly regulated these processes. The initial phase of the implantation process is "adplantation." This first phase requires the newly hatched blastocyst to loosely adhere to the endometrial epithelium, often "rolling" to the eventual site of implantation where it firmly adhered. This process requires both the blastocyst adhesion interaction with the endometrium during the "receptive window.[16] In many mammalian species, the processes of early pregnancy occur in a hypoxic environment. However, the mechanisms underlying maternal adaptation to hypoxia during early pregnancy remain unclear.[17] Also, N-glycosylation of uterine endometrium determines its receptivity. Glycosylation alters the molecular and functional features of glycoproteins, which is closely related to many physiological processes and diseases.[18] Single-cell RNA sequencing of cells from cultured human blastocysts has enabled us to define the transcriptomic landscape of placental trophoblast (TB) that surrounds the epiblast and associated embryonic tissues during the enigmatic day 8 (D8) to D12 peri-implantation period before the villous placenta forms.[19] The decidual cells secrete many interleukins, growth factors, and other factors that can be classified as either supporting implantation (pro-invasive) or inhibiting (anti-invasive). Pro-invasive factors - IL-1β, IL-5, IL-6, IL-7, IL-8, IL-9, IL-13, IL-15, Eotaxin CCL11, IP-10 and RANTES. Anti-invasive factors - IL-10, IL-12 and VEGF.[20] Recent studies have shown a negative effect of CE on implantation by impairing decidualization.[21] CE has attracted much attention among fertility care providers and scientists because it has been potentially associated with reproductive issues in the last decades. Several studies have shown a high prevalence of CE among women with recurrent IVF failures (13.95 - 57.55%), unexplained infertility (UEI) (40.7-55.7%), and repeated loss of early pregnancy (42.9-56%).[22,23] Several authors recently have studied the possible mechanisms of the endometrium re-

productive health hampered by CE. Improvement in technology and increased training has led to widespread use of hysteroscopy, and it has become the method of choice for the diagnosis and treatment of intrauterine pathologies. During operative hysteroscopy, uterine perforation, bleeding, and air emboli because of used distention medium and hyponatremia which resulted from infusion of large amounts of distention medium into circulation and allergic reactions may occur.[24] The present study aims to assess the incidence of CE in women with UEI and RIF depending on hysteroscopic findings.

## MATERIALS and METHODS

This cross-sectional retrospective study was done on 529 participants who attended our hospital's infertility clinic between January 2014 and August 2020. The participants were at the age of 18-39 years. We divided the subjects into two groups, i.e., unexplained infertile cases with RIF (Group:1;n:187) and unexplained infertile cases without RIF (Group:2;n:342). They had no additional chronic illnesses like thyroid problems, diabetes or hypertension. All of the participants had unexplained infertility. All patients have undergone hysteroscopy. Demographical and clinical characteristics, including age, body mass index (BMI), total dosage of used gnd, duration of stimulation, total number of retrieved oocytes, Anti mullerian hormone (AMH), smoking, hysteroscopic findings were compared. The participants submitted the informed consent. This study was approved by the Ethics Committee of Beykoz University, Turkey (Date: 06.11.2020-Decision No: 2020/3). All procedures conducted in studies, including human participants, conformed to ethical standards of the national or institutional research committee and the Helsinki Declaration 1964 and subsequent amendments or other ethical standards.

### Statistical Analysis

SPSS version 26.0 (SPSS Inc., Chicago, IL, USA) was applied to perform statistics. The Kolmogorov–Smirnov test results show that all quantitative variables are not normally distributed. The relationship between the quantitative variables in the two groups is studied using the Mann–Whitney test. The factors of group exposure were assessed using logistic regression analysis. In this case, in which we have zero events in a subgroup, penalized maximum likelihood estimation was used.

## RESULTS

This study sample consisted of 529 participants (187 cases with RIF and 342 without RIF) with unexplained infertility. Table 1 shows the descriptive statistics of the variables.

**Table 1.** Descriptive statistics of the variables

| Variable | n | Minimum | Maximum | Mean | Sd |
|---|---|---|---|---|---|
| Female Age (y) | 529 | 18 | 39 | 31.6 | 5.1 |
| BMI(body mass index) | 529 | 18 | 33 | 24.6 | 2.5 |
| Total use of gonadotropin(IU) | 529 | 900 | 3000 | 2146.9 | 312.5 |
| Duration of stimulation(days) | 529 | 7 | 12 | 9.99 | 0.98 |
| Number of retrieved oocytes | 529 | 7 | 13 | 8.1 | 0.6 |
| AMH(ng/ml) | 529 | 1 | 3.81 | 1.43 | 0.6 |
| MII | 529 | 6 | 10 | 6.2 | 0.6 |
| PN | 529 | 5 | 8 | 6.005 | 0.3 |

| Variable | Frequency | Percent |
|---|---|---|
| **Infertility type** | | |
| Primary | 370 | 69.9 |
| Secondary | 159 | 30.1 |
| **Smoking** | | |
| No | 457 | 86.4 |
| Yes | 72 | 13.6 |
| **Hysteroscopical Findings** | | |
| Chronic Endometritis | 14 | 2.6 |
| Polyps | 19 | 3.6 |
| No pathology | 496 | 93.8 |
| **Group** | | |
| With recurrent implantation failure (Group:1) | 187 | 35.3 |
| Without recurrent implantation failure (Group:2) | 342 | 64.7 |

AMH: Anti-Mullerian Hormone, BMI: body mass index, MII: Metaphase II, PN: Pronucleus

As Table 1 shows, the participants have a mean age of 31.6 years ±5.1. The mean BMI of the participants is 24.6±2.5. The total use of gonadotropin is 2146.9±312.5. The mean duration of stimulation is 9.99±0.98 days. The mean AMH level is 1.43±0.6. The total number of retrieved oocytes is 8.1±0.6. The mean number of MII and PN are 6.2±0.6 and 6.005±0.3, respectively. Of 370 (69.9%) women have primary and 159 women (30.1%) have secondary infertility. 457 subjects (86.4%) are not smokers. The hysteroscopy findings showed that 14(2.6%) have CE, 19(3.6%) have endometrial polyps, and 496 (93.8%) have no endometrial pathology.

Table 2 shows the relationship between the studied variables in both groups using Mann-Whitney Test.

**Table 2.** Comparison of two groups using Mann-Whitney test

| Variable | Group | | p |
|---|---|---|---|
| | Group:1 (n:187) Mean (Sd) | Group:2 (n:342) Mean (Sd) | |
| Age female(y) | 31.8(4.5) | 31.6(5.7) | 0.4 |
| BMI(kg/m$^2$) | 24.7(2.5) | 24.6(2.6) | 0.7 |
| AMH(ng/ml) | 1.4(0.5) | 1.4(0.6) | 0.8 |
| Total dose of gonadotropin (IU) | 2113.8 (420.6) | 2165.05 (231.9) | 0.6 |
| Duration of stimulation (days) | 9.9 (0.9) | 10.03 (1.01) | 0.06 |
| Number of retrieved oocytes | 8.03(0.3) | 8.1(0.7) | 0.1 |
| MII | 6.4(0.8) | 6.1(0.5) | 0.06 |
| PN | 5.9(0.1) | 6.02(0.4) | 0.7 |

MII:Metaphase II,PN:Pronucleus

Table 2 shows no significant difference in BMI, age, AMH level, total dose of gonadotropin, duration of stimulation, number of retrieved oocytes, MII, and PN between the two groups.

Table 3 shows the relationship between the variables studied in both groups using Chi-Square and exact Fisher Tests.

**Table 3.** The relationship between the studied variables in both groups using Chi-Square and exact Fisher Tests

| Variable | Group | | p |
|---|---|---|---|
| | Group:1 (n:187) frequency (%) | Group:2 (n:342) frequency (%) | |
| **Infertility type** | | | 0.09 |
| Primary | 122(65.2) | 248(75.2) | |
| Secondary | 65(34.8) | 94(27.5) | |
| **Number of trial** | | | <0.001 |
| 1.00 | 0 | 119(34.8) | |
| 2.00 | 0 | 223(65.2) | |
| 3.00 | 141(75.4) | 0 | |
| 4.00 | 28(15) | 0 | |
| 5.00 | 16(8.6) | 0 | |
| 6.00 | 2(1.1) | 0 | |
| **Smoking** | | | 0.5 |
| No | 161(86.1) | 296(86.5) | |
| Yes | 26(13.9) | 46(13.5) | |

Table 3 shows that the two groups show no statistically significant difference in infertility type (P=0.09) and smoking(P=0.5). The two groups are statistically significantly different in the number of trial (p=0.000).

Table 4 shows the relationship between the hysteroscopic variables of both groups using Chi-Square and exact Fisher Tests.

**Table 4.**The comparison of hysteroscopic findings in both groups

| Variable | Group | | p |
|---|---|---|---|
| | Group:1 (n:187) frequency (%) | Group:2 (n:342) frequency (%) | |
| **Hysteroscopy** | | | 0.01 |
| Chronic Endometritis | 10(5.3) | 4(1.2) | 0.1 |
| Polyps | 9(4.8) | 10(2.9) | 0.8 |
| No endometrial pathology | 168(89.9) | 328(95.9) | <0.001 |

Table 4 shows that the two groups show no statistically significant difference in CE (p=0.1) and polyps (p=0.8), while the two groups are statistically significantly different in the presence of endometrial pathology(p=0.000). The results of the study showed that those women who had RIF did not show a higher incidence of CE, but endometrial pathologies (EP) were increased in this group of patients.

Table 5 shows the logistic regression analyses for some risk factors and chronic endometritis.

**Table 5.** Logistic regression analyses for some risk factors and chronic endometritis

| Variable | OR (95%CI) | p |
|---|---|---|
| **Female Age** | 1(0.97,1.04) | 0.7 |
| **BMI** | 0.9(0.9,1.05) | 0.6 |
| **Total dose of gonadotropin** | 1(0.99,1) | 0.07 |
| **Duration of stimulation** | 1.12(0.9,1.3) | 0.2 |
| **Number of retrieved oocytes** | 1.5(1.04,2.16) | 0.02 |
| **AMH** | 1.08(0.8,1.4) | 0.6 |
| **MII** | 0.5(0.4,0.6) | 0.000 |
| **PN** | 1.35(0.8,2.22) | 0. |
| **Infertility type** | | |
| 1.00 | | |
| 2.00 | | |
| **Total number of trial** | | |
| 1.00 | 1 | |
| 2.00 | 1.87(0.03-94.8) | 0.7 |
| 3.00 | 0.00001(2.91e-07-0.0007) | 0.000 |
| 4.00 | 0.00007(1.43e-06-0.003) | 0.000 |
| 5.00 | 0.0001(2.43e-06-0.006) | 0.000 |
| 6.00 | 0.0008(0.00001-0.05) | 0.001 |
| **Smoking** | | |
| No | 0 | |
| Yes | 0.95(0.57-1.59) | 0.8 |
| **Hysteroscopy** | | |
| Chronic Endometritis | 1 | |
| Polyps | 2.57(0.6-1.5) | 0.1 |
| Diagnostic | 4.5(1.4-13.9) | 0.008 |
| **Embryo transfer** | | |
| 1.00 | 1 | |
| 2.00 | 0.05(0.01-0.19) | 0.000 |

AMH: Anti-Mullerian Hormone, BMI:body mass index,MII:Metaphase II,PN:Pronucleus

In Table 5,Age, BMI, total dose of gonadotropin, duration of stimulation, AMH, and smoking were not the significant risk factors for chronic endometritis. Regarding the association between the risk factors and prevalence of the CE, the total number of oocytes was associated with the increased risk of CE(OR=1.5), MII was associated with the decreased risk of CE(OR=0.5).

## DISCUSSION

Implantation is the result of a complex interaction between the blastocyst and the endometrium. Different signaling pathways participate in this unique biological link and an appropriate endometrium is requested for the implantation success. Many pathologies of the endometrium and uterus affect endometrial receptivity. The potential mechanisms whereby endometrial polyps could adversely impact fertility include both mechanical interference and the release of molecules that adversely affect sperm transport or embryo implantation. There exists evidence of increased levels of glycodelin,[25] aromatase[26] inflammatory markers,[27] and reduced levels of HOXA-10 and -11 messenger RNA.[28] (No studies were found comparing these expressions before and after polypectomy. Adenomyosis on the molecular expressions is thought to be important for optimal endometrial receptivity. Decreased Hox-A10 gene expression, LIF dysregulation, downregulation of NR4A and FOXO1A and increased levels of IL-1b,corticotropin-releasing hormone), NK cells, macrophages, and a spectrum of cytokines are seen.[29] In myomas also, Hox-A10 gene expression decreases. Especially, submucous leiomyomas produce substances that can alter the endometrial milieu in the midluteal phase in a way that is associated with reduced implantation success.[29] Several studies have been done on the effect of endometritis, especially CE, on human pregnancy in the last decade and most of them showed the potential association. The present study aimed to assess the CE incidence in unexplained infertile women with RIF depending on hysteroscopic findings. The findings showed that those who had RIF did not show an increased frequency of CE. In other words, CE incidence was similar in UEI patients with or without RIF. Considerable efforts have been made recently to clarify the relationship between CE and infertility, helping manage women suffering from a poor reproductive outcome.[30] Song et al. found an association between CE and undesirable reproductive outcomes, including implantation failure and recurrent loss of pregnancy.[31] CE has the prevalence of varying between 1.4 % among those with non-normal uterine bleeding and 56% in those with recurrent pregnancy loss and infertility,[32] while our study did not find any association between CE and RIF. Cicinelli et al. found that a reliable diagnostic characteristic of CE is the presence of micropolyps during hysteroscopy.[33] It has been found that several women experiencing RIF have CE due to bacterial colonization, which has the lowest or no symptoms of infection.[13] Kushnir et al. found CE in 45% of the infertile patients, particularly those who had RIF, which is not consistent with our study results.[34] Matteo et al. state that CE impedes endometrial receptivity and consequently leads to infertility since the endometrium is characterized by abnormal inflammatory mediators and an aberrant endometrial microenvironment in the endometrial lining, such as cytokines, leukocytes, and immunoglobulins.[35] A body of evidence found the adverse effect of CE on pregnancy outcome by disordering the endometrial microenvironment and hampering endometrial receptivity.[15,36] The infertile subjects who have endometrial polyps have more prevalent CE than fertile women. The infertile subjects with cured CE had the same pregnancy outcome as the infertile ones without CE. According to multivariate analysis, there is a significant association between infertility and diagnosis of CE among those with EP.[37] Despite the lack of comparison between fertile and infertile groups, the previous studies have shown that infertile women experienced a high CE prevalence, which is not in line with our study results.[8] CE reversibly causes infertility, and its recognition and treatment may improve the chances at the next IVF attempts and may improve the outcome of IVF among those with RIF.[23] Sfakianoudis et al. have found an association between CE and infertility and RIF, which does not support our study findings.[2] Saxtorph et al. conducted endometrial investigations and found that chronic endometritis was more prevalent in the RIF cohort.[37,38] EC has been associated with RIF in some trials, which is prevalent between 8 and 57%, depending on the diagnosis criteria, and those with RIF were found to have more prevalent endometrial dysfunction biomarkers, which is not in line with our study results.[12,23] Johnston et al. found a signifi-

cantly lower implantation rate among the non-fertile women with RIF and CE during the IVF-ET cycle following endometrial biopsy than women with RIF but not with CE (15% vs. 46%), and there is an association between CE and poor reproductive outcomes, including RPL and implantation failure, which is not in line with our study results.[39] Also, in the study of Tanacan et al., it was shown that performing diagnostic hysteroscopy prior to the first IVF treatment cycle without correcting any anatomic abnormalities did not improve live birth rates(LBRs).[40]

The low number of patients and retrospective study design were among the limitations of our study. In this study, those with RIF did not show a higher incidence of CE, but endometrial pathologies were increased in this group of patients. So hysteroscopy should be a part of our work-up in RIF patients with unexplained infertility.

**Conflict of Interest**

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

**Authors' Contributions**

Concept/Design: NDG, TG, AY. Data Collection and/or Processing: NDG, TG, AY. Data analysis and interpretation: NDG, TG, AY. Literature Search: NDG, TG, AY. Drafting manuscript: NDG, TG, AY. Critical revision of manuscript: NDG, TG, AY. Supervision: NDG, TG, AY.

**REFERENCES**


1. Puente E, Alonso L, Laganà AS, Ghezzi F, Casarin J, Carugno J. Chronic endometritis: old problem, novel insights and future challenges. Int J Fertil Steril. 2020;13(4):250-256.
2. Sfakianoudis K, Simopoulou M, Nitsos N, et al. Successful implantation and live birth following autologous platelet-rich plasma treatment for a patient with recurrent implantation failure and chronic endometritis. In Vivo. 2019;33(2):515-521.
3. Kimura F, Takebayashi A, Ishida M, et al. Chronic endometritis and its effect on reproduction. J Obstet Gynaecol Res. 2019;45(5):951-960.
4. Kitaya K, Matsubayashi H, Takaya Y, et al. Live birth rate following oral antibiotic treatment for chronic endometritis in infertile women with repeated implantation failure. Am J Reprod Immunol. 2017;78(5): e12719.
5. Greenwood SM, Moran JJ. Chronic endometritis: morphologic and clinical observations. Obstet Gynecol. 1981;58(2):176-184.
6. Park HJ, Kim YS, Yoon TK, Lee WS. Chronic endometritis and infertility. Clin Exp Reprod Med. 2016;43(4):185-192.
7. Kitaya K, Yasuo T. Aberrant expression of selectin E, CXCL1, and CXCL13 in chronic endometritis. Mod Pathol. 2010;23(8):1136-1146.
8. Cicinelli E, Matteo M, Trojano G, et al. Chronic endometritis in patients with unexplained infertility: prevalence and effects of antibiotic treatment on spontaneous conception. Am J Reprod Immunol. 2018; 79(1):e12782.
9. McQueen DB, Perfetto CO, Hazard FK, Lathi RB. Pregnancy outcomes in women with chronic endometritis and recurrent pregnancy loss. Fertil and Steril. 2015;104(4):927-931.
10. Takebayashi A, Kimura F, Kishi Y,et al. The association between endometriosis and chronic endometritis. PLoS One. 2014;9(2):e0088354.
11. Bashiri A, Halper KI, Orvieto R. Recurrent Implantation Failure-update overview on etiology, diagnosis, treatment, and future directions. Reprod Biol Endocrinol. 2018;16(1):1-8.
12. Bouet PE, El Hachem H, Monceau E, Gariépy G, Kadoch IJ, Sylvestre C. Chronic endometritis in women with recurrent pregnancy loss and recurrent implantation failure: prevalence and role of office hysteroscopy and immunohistochemistry in diagnosis. Fertil and Steril. 2016;105(1):106-110.
13. Cicinelli E, Matteo M, Tinelli R, et al. Prevalence of chronic endometritis in repeated unexplained implantation failure and the IVF success rate after antibiotic therapy. Hum Reprod. 2015;30(2):323-330.
14. Kitaya K, Tada Y, Hayashi T, Taguchi S, Funabiki M and Nakamura Y: Comprehensive endometrial immunoglobulin subclass analysis in infertile women suffering from repeated implantation failure with or without chronic endometritis. Am J Reprod Immunol. 2014;72 (4):386-391.
15. Zhang Y, Xu H, Liu Y, et al. Confirmation of chronic endometritis in repeated implantation failure and success outcome in IVF-ET after intrauterine delivery of the combined administration of antibiotic and dexamethasone. Am J of Reprod Immunol. 2019;82 (5):e13177.
16. Griffith OW, Chavan AR, Protopapas S, et al. Embryo implantation evolved from an ancestral inflammatory attachment reaction. Proc. Natl. Acad. Sci. 2017;114 (32):E6566-6575.
17. Bhurke A, Kannan A, Ma O, et al. A hypoxia-induced Rab pathway regulates embryo implantation by controlled trafficking of secretory granules. Proc Natl Acad Sci. 2020;117(25):14532-14542.
18. Yu M, Qin H, Wang H, et al. N-glycosylation of uterine endometrium determines its receptivity. J. Cell. Physiol. 2020;235(2):1076-1089.
19. West RC, Ming H, Logsdon DM, et al. Dynamics of trophoblast differentiation in peri-implantation-stage human embryos. Proc. Natl. Acad. Sci. 2019;116(45): 22635-22644.
20. Cha J, Sun X & Dey SK. Mechanisms of implantation: strategies for successful pregnancy. Nat. Med. 2012; 18(12):1754-1767.
21. Franasiak JM. Chronic endometritis is associated with an altered microbiome, but what about treatment and clinical outcomes?. Fertil Steril. 2019;112(4):649-650.
22. Vitagliano A, Noventa M, Gizzo S. Autoimmunity, systemic inflammation, and their correlation with repeated implantation failure and recurrent miscarriage: is chronic endometritis the missing piece of the jigsaw?. Am J Reprod Immunol. 2017;77(1):1-2.
23. Vitagliano A, Saccardi C, Noventa M, et al. Effects of chronic endometritis therapy on in vitro fertilization outcome in women with repeated implantation failure: a systematic review and meta-analysis. Fertil Steril. 2018;110(1):103-112.
24. Valle R.F.: "Development of hysteroscopy from a dream to a reality and its linkage to the present and future". J. Minim. Invasive Gynecol. 2007;14:407.

25. Richlin SS, Ramachandran S, Shanti A, et al. Glycodelin levels in uterine flushings and in plasma of patients with leiomyomas and polyps: implications for implantation. Hum Reprod. 2002;17(10):2742-2747.
26. Maia H Jr, Pimentel K, Silva TM, et al. Aromatase and cyclooxygenase-2 expression in endometrial polyps during the menstrual cycle. Gynecol Endocrinol. 2006;22(4):219-224.
27. Ben-Nagi J, Miell J, Yazbek J, et al. The effect of hysteroscopic polypectomy on the concentrations of endometrial implantation factors in uterine flushings. Reprod Biomed Online. 2009;19(5):737-744.
28. Rackow BW, Jorgensen E, Taylor HS. Endometrial polyps affect uterine receptivity. Fertil Steril. 2011;95(8):2690-2692.
29. Munro, MG Uterine polyps, adenomyosis, leiomyomas, and endometrial receptivity. Fertility and Sterility. 2019;111(4):629-640.
30. Huang W, Liu B, He Y, et al. Variation of diagnostic criteria in women with chronic endometritis and its effect on reproductive outcomes: A systematic review and meta-analysis. J Reprod Immunol. 2020;140: 103146.
31. Song D, Li TC, Zhang Y, et al. Correlation between hysteroscopy findings and chronic endometritis. Fertil Steril. 2019;111(4):772-779.
32. Kitaya K, Takeuchi T, Mizuta S, Matsubayashi, H Ishikawa T Endometritis: new time, new concepts. Fertil Steril. 2018;110(3):344-350.
33. Cicinelli E, Resta L, Nicoletti R, et al. Detection of chronic endometritis at fluid hysteroscopy. J Minim Invasive Gynecol. 2005;12(6):514-518.
34. Kushnir VA, Solouki S, Sarig-Meth T, et al. Systemic inflammation and autoimmunity in women with chronic endometritis. Am J Reprod Immunol. 2016;75(6): 672-677.
35. Matteo M, Cicinelli E, Greco P, et al. Abnormal pattern of lymphocyte subpopulations in the endometrium of infertile women with chronic endometritis. Am J Reprod Immunol. 2009;61(5):322-329.
36. Altmäe S, Mendoza-Tesarik R, Mendoza C, Mendoza N, Cucinelli F, Tesarik J. Effect of growth hormone on uterine receptivity in women with repeated implantation failure in an oocyte donation program: a randomized controlled trial. J Endocr Soc. 2018;2(1):96-105.
37. Saxtorph MH, Hallager T, Persson G, et al. Assessing endometrial receptivity after recurrent implantation failure: a prospective controlled cohort study. Reprod Biomed Online. 2020;41(6):998-1006.
38. Liu Y, Chen X, Huang J, et al. Comparison of the prevalence of chronic endometritis as determined by means of different diagnostic methods in women with and without reproductive failure. Fertil. Steril. 2018;109(5):832-839.
39. 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):437–441.
40. Tanacan A, Mumusoglu S, Yaralı H, et al. The effect of performing hysteroscopy prior to the first in vitro fertilization (IVF) cycle on live birth rate. Gynecol Endocrinol. 2019;35(5):443-447.