Brief Report

# Comparing the Frequency of Endometritis in Unexplained Infertility and Anovulatory Infertility

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## Abstract

**Background:** Acute pelvic inflammatory disease (PID) is a common reason for infertility. This study aimed to evaluate the frequency distribution of endometritis in women with unexplained infertility and comparison with frequency distribution of endometritis in anovulatory infertility to identify the importance of endometritis due to subacute PID evaluation in the case of infertility. **Materials and Methods:** This case–control study was done on 100 women with unexplained infertility and ovulatory infertility who referred to Shahid Beheshti clinic in 2013 in Isfahan, Iran. They were divided into two groups of unexplained infertility and anovulatory infertility. Endometrial samples were given from all the patients by Pipelle biopsy under sterile conditions, and then prepared samples were sent to the pathology laboratory to evaluate the existence of plasma cells by a pathologist to diagnose endometritis. **Results:** Frequency distribution of acute PID history among the patients in both groups showed a significant difference ($P < 0.05$). Prevalence of endometritis in unexplained infertility group was 34% and in anovulatory group was 21% ($P < 0.05$). Prevalence of vaginitis was 46% in unexplained group and 40% in anovulatory group ($P < 0.05$), and prevalence of PID was 4% in unexplained infertility group and 0% in anovulatory infertility group. **Conclusion:** The prevalence of endometritis and vaginitis was more in the unexplained infertility group rather than the anovulatory infertility group that may reveal the importance of endometritis evaluation in the cases of unexplained infertility.

**Keywords:** *Anovulatory infertility, endometritis, subacute pelvic inflammatory disease, unexplained infertility, vaginitis*

## Introduction

An infertility evaluation is usually initiated after 1 year of regular unprotected intercourse in women under age 35 years and after 6 months of unprotected intercourse in women age 35 years and older. However, the evaluation may be initiated sooner in women with irregular menstrual cycles or known risk factors for infertility such as endometriosis, a history of pelvic inflammatory disease (PID), or reproductive tract malformations.[1]

Endometritis refers to inflammation of the endometrium, the inner lining of the uterus. Pathologists have traditionally classified endometritis as either acute or chronic. Acute endometritis is characterized by the presence of microabscesses or neutrophils within the endometrial glands, whereas chronic endometritis (CE) is distinguished by a variable number of plasma cells within the endometrial stroma.[2]

In the absence of a tissue sample, other factors can help distinguish between acute and chronic endometrial inflammation. Symptoms alone are not useful since the clinical manifestations of both disorders are similar (abnormal vaginal bleeding and pelvic pain). Acute endometritis in the nonobstetric population is usually preceded by PID either secondary to a sexually transmitted infection or an invasive gynecologic procedure.[1,2] Although extensive endometriosis involving the tubes and distorting the ovary are clearly likely to interfere with egg transport and ovulation, it is less clear how mild to moderate endometriosis exerts an effect on fertility.[3]

Endometriosis is a common medical condition that sometimes leads to the formation of scar tissue and infertility. It is present in 5%–10% of fertile women and in 10%–50% of those presenting with infertility in Western countries. Female infertility has important medical, social, and economic consequences worldwide.[4]

Vaginitis is very common disease in women in productive year that is recognized with

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amination and observation of physicians to diagnose if it is bacterial or fungal. Sexually transmitted disease (STD) refers to disease that transfer by sexual activity.[1-4]

PID refers to acute infection of the upper genital tract structures in women, involving any or all of the uterus, oviducts, and ovaries; this is often accompanied by involvement of the neighboring pelvic organs. Involvement of these structures results in endometritis, salpingitis, oophoritis, peritonitis, perihepatitis, and tubo-ovarian abscess.[5]

According to a National Ambulatory Medical Care Survey, the estimated number of cases of PID in women 15–44 years of age in the United States decreased from 189,662 in 2002 to 168,837 in 2003. The number of hospitalizations for acute PID steadily declined from approximately 70,000 cases/year in 1998 to 45,000 cases/year in 2007. Visits to physicians' offices for PID also have declined, primarily due to aggressive population-based chlamydia screening and treatment programs nationwide.[5,6]

The last 30 years have witnessed an interesting, if circular, evolution of the clinical approach to the diagnosis of PID. Diagnostic procedures to document PID at one time replaced a primary clinical diagnosis. It is now appreciated that PID represents a spectrum of infection that there is no single diagnostic gold standard and that the practical value of clinical diagnosis retains central importance.[7]

At one time, infertility due to female factors was thought to be the reason behind all fertility problems. Today, experts recognize that female infertility accounts for about 40% of all infertility cases, whereas male infertility accounts for 40%–50% of cases, with the most common reasons being tubal blockages, ovulation problems, and endometriosis. Unfortunately, around 15%–20% of cases have no obvious cause associated with them, leading to a diagnosis of unexplained infertility.[8]

The most common cause of blocked tubes is infection, and the most common infection implicated is chlamydia. About 70% of women who have blocked tubes have had a chlamydia infection though half the time, it will have been silent and they will not have even been aware of it.[4]

Apart from being terribly frustrating, unexplained infertility means that treatment is not directed at any known cause. Approximately, 60% of couples with unexplained infertility of <3 years duration will fall pregnant in the next 3 years without any treatment at all. Recent analysis of all the studies of clomiphene has not found it to be beneficial.[8,9]

In previously published studies, acute PID has been evaluated in infertility, but in this study, we evaluated subclinical PID that has no sign in patient and would be recognized by Pipelle smear.

This study aimed to evaluate the frequency distribution of endometritis in the women with unexplained infertility and comparison with frequency distribution of endometritis in anovulatory infertility to identify the importance of endometritis evaluation in the case of infertility.

## Materials and Methods

This case–control study was done on 100 women with unexplained infertility and ovulatory infertility that were selected from all the patients with infertility referred to Shahid Beheshti clinic in 2013 in Isfahan, Iran, and were divided into two groups of unexplained infertility and anovulatory infertility.

We explained the study and procedure and asked permission from all the patients to participate.

There were fifty women in each group. The first group consisted of women with unexplained infertility and the second included the ones with anovulatory infertility based on Pipelle test and a pathologist diagnosis mentioned in their documents.

The inclusion criteria included having unexplained or anovulatory gynecologist-proved infertility, age between 20 and 35 years, no treatment for endometritis, and consent to participate in the study. Cases with no interest to cooperate were excluded in any phase of the study. All of the patient that consumed antibiotic for vaginitis or acute PID or managed with IVF or IUI, someone who had male factor infertility and all the cases with induction ovulation and history of acute PID were also excluded from the study.

All the patients were asked to fill the questionnaire to get the information about any clinical symptoms such as dyspareunia, vaginitis, history of PID, and the way of treatment and the used drugs' doses. They were previously informed about the study procedure and stated their satisfaction to participate.

Endometrial samples were taken from all the patients by Pipelle biopsy under sterile conditions, and then prepared samples were sent to the pathology section to evaluate the existence of plasma cells by a pathologist to diagnose endometritis. All samples were evaluated by another pathologist who worked in Shahid Beheshti Hospital.

STDs were diagnosed with physical examination and past history of patient. PID was recognized with signs and symptoms that have been explained, and vaginitis was recognized with speculum examinations and observations.

Women with anovulation have been considered as irregular periods or, in the worst case, they may not get their cycles at all. If the cycles were shorter than 21 days or longer than 36 days, they may have ovulatory dysfunction. Furthermore, if their cycles fall within the normal range of 21–36 days, but the length of the cycles varies widely from month to month that may also be a sign of ovulatory dysfunction (for example, 1 month period is 22 days,

the next it is 35.). It is possible to get the cycles on an almost normal schedule and not ovulate though this is not common. A menstrual cycle where ovulation does not occur is called an anovulatory cycle.

STDs are caused by infections that are passed from one person to another during sexual contact. These infections often do not cause any symptoms. Medically, infections are only called diseases when they cause symptoms. That is why STDs are also called "sexually transmitted infections." However, it is very common for people to use the terms "sexually transmitted diseases" or "STDs," even when there are no signs of disease. There are many kinds of STDs and infection, and they are very common as more than half of all of us will get one at some time in our lives. Its signs and symptoms may include painful urination, lower abdominal pain, vaginal discharge in women, and discharge from the penis in men.

All the participants have been evaluated about these kinds of diseases by a gynecologist and all the needed tests have been done.

Data were gathered and analyzed by SPSS version 20 software (SPSS Inc. 233 South Wacker Drive, 11th Floor Chicago, IL 6066412) using Fisher's exact test and *t*-test.

## Results

The mean age of the patients in unexplained infertility group was 30.24 ± 4.7 years and 32.84 ± 5.2 in anovulatory infertility group, with no significant difference; these two groups were similar in age and the other basic characteristics [Table 1].

The frequency distribution of endometritis in unexplained infertility group was much more rather than anovulatory group with a significant difference ($P = 0.015$).

Frequency distribution of acute PID history among the patients in both groups showed a significant difference ($P = 0.041$) [Table 2].

**Table 1: Basic characteristics of the two groups**

| Variables | Unexplained infertility | Anovulatory infertility | *P* |
|---|---|---|---|
| Age (years) | 22-35 | 22-35 | >0.05 |
| Economic status | Moderate | Moderate | |
| Infertility history | >1 year | >1 year | >0.05 |
| Induction ovulation | Done | Done | |
| PID management | Negative | Negative | >0.05 |

PID: Pelvic inflammatory disease

**Table 2: Comparison of the frequency distribution of studied factors in the both groups**

| Variable | *n* (%) | | *P** |
|---|---|---|---|
| | Unexplained infertility (*n*=50) | Anovulatory infertility (*n*=50) | |
| Endometritis | | | |
| No | 16 (32) | 29 (58) | 0.015 |
| Yes | 34 (68) | 21 (42) | |
| Vaginitis | | | |
| No | 4 (8) | 10 (20) | 0.148 |
| Yes | 46 (92) | 40 (80) | |
| STD | | | |
| No | 10 (20) | 12 (24) | 0.810 |
| Yes | 40 (80) | 38 (76) | |
| PID | | | |
| No | 46 (92) | 50 (100) | 0.041 |
| Yes | 4 (8) | 0 | |

*Used of Fisher's exact test. PID: Pelvic inflammatory disease, STD: Sexually transmitted disease

## Discussion

PID, the infection and inflammation of a woman's fallopian tubes (salpingitis) and uterine lining (endometritis), is considered to cause infertility, ectopic pregnancy, chronic pelvic pain (CPP), and recurrent PID. Evidence for this comes from the Lund, Sweden, cohort study, in which among 1844 women with clinically suspected PID, salpingitis verified by laparoscopy was associated with infertility, ectopic pregnancy, recurrent PID, and CPP.[10]

Previous studies, mostly from the United States, have investigated the association between ethnicity and PID, endometriosis, and the use of infertility services. From a public health point of view, it is important to identify population groups that have an increased risk of diseases that could cause infertility.[11] However, to the best of our knowledge, no previous study has had the opportunity to compare the existence of endometritis in population of infertile women.

A smaller retrospective study of 51 women with a hospital discharge diagnosis of PID, salpingitis, or tubo-ovarian abscess reported similarly increased risks of adverse sequelae although associations were borderline or not significant. These studies, plus a number of retrospective case–control reports, in which women with tubal occlusion were more likely to bear chlamydial or gonococcal antibodies, provide the human evidence supporting a causal link between PID and infertility.[8,9]

In a study by Haggerty *et al*. on 614 women in the PID Evaluation and Clinical Health (PEACH) study with pelvic pain, pelvic organ tenderness, and leukorrhea, mucopurulent cervicitis or untreated cervicitis, they were compared in endometritis (≥5 neutrophils or ≥2 plasma cells), *Neisseria gonorrhoeae* or chlamydia trachomatis upper genital tract infection (UGTI) or both to women without endometritis/UGTI for outcomes of pregnancy, infertility, recurrent PID, and CPP. The results showed that endometritis/UGTI was not associated with reduced

pregnancy (odds ratio [OR] 0.8, 95% confidence interval [CI] 0.6–1.2) or elevated infertility (OR 1.0, 95% CI 0.6–1.6), recurrent PID (OR 0.6, 95% CI 0.4–0.9), or CPP (OR 0.6, 95% CI 0.4–0.9).[10]

In our study, regarding the high prevalence of vaginitis in the both groups, this factor cannot be considered as a subclinical PID sign and also it was shown by STD treatment procedures that custom STD treatment cannot be led to low the effects of PID on endometria.

In another study, 92 women with clinical signs and symptoms of mild-to-moderate PID, enrolled in the PEACH study, were evaluated. For all human leukocyte antigen Class II DQ alleles with a prevalence of 10% or greater in the population, demographics, cervical infections, endometrial pathology, and fertility outcomes were assessed. The results of this study showed that chlamydial cervicitis, gonococcal cervicitis, endometritis, and infertility were all more common among women carrying the DQA *0301 allele after adjustment for race. Endometritis and infertility were somewhat less common (or pregnancy more common) among women carrying the DQA *0501 and DQB *0402 alleles. Hence, it may say that among women with signs and symptoms of PID, carriage of the DQA *0301, DQA *0501, and DQB *0402 alleles altered the occurrence of lower genital tract infection, upper genital tract inflammation, and infertility.[12]

In a cohort study in Sweden, a total of 2,170,177 women living in Sweden at some point between 1990 and 2004, categorized into ten different groups according to the country of birth were evaluated for PID and infertility, all groups of foreign-born women exhibited significantly increased risks compared with Swedish-born women. The highest risks of PID were found among women from southern Europe, Eritrea/Ethiopia/Somalia, and other African countries, whereas the highest risks of infertility were found among women from Middle Eastern countries, other Asian countries, and other African countries. Compared with PID and infertility, country of birth was less associated with endometriosis and EP although some differences were found. Even in a country like Sweden, which offers publicly financed treatment for infertility, differences based on country of birth exist. Although data on partners' income were not available to us, it is possible that other factors besides socioeconomic factors are present in the etiology of female health problems related to infertility.[11]

Johnston-MacAnanny *et al*. in a study on 33 patients with recurrent implantation failure (RIF) who underwent endometrial sampling and subsequent embryo transfer (ET) were analyzed based on immunohistochemically confirmed CE: CE present on biopsy (Group 1; $n$ = 10) and CE absent on biopsy (Group 2; $n$ = 23). Patients with RIF undergoing IVF cycles during the same time period who did not have endometrial sampling were used as controls (Group 3; $n$ = 485). According to the results of this study, CE was identified in 30.3% of patients with RIF. Group 1 had lower implantation rates (11.5%) in the IVF cycle following treatment than did Groups 2 and 3 (32.7% and 20.3%, respectively). Women demonstrating CE on endometrial sampling have lower implantation rates in a subsequent *in vitro* fertilization-ET cycle; however, there were no differences in subsequent clinical pregnancy or ongoing pregnancy rates after successful antibiotic treatment.

According to the results of the current study, it seems that subclinical PID is not exactly followed by acute PID and it may be a person with subclinical PID without acute disease and it can entangle the endometria and the other organs without a certain sign.

## Conclusion

The results of this study showed that the prevalence of endometritis and vaginitis was more in the unexplained infertility group rather than the anovulatory infertility group, so it may reveal the importance of endometritis evaluation in the cases of unexplained infertility. According to the achieved results from the present work, it seems that subclinical PID is not certainly followed by acute PID and it may be induced without an acute disease.

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### Conflicts of interest

There are no conflicts of interest.

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