Austin Journal of Obstetrics and Gynecology

Open Access

Austin Publishing Group

Research Article

# The Role of Chlamydial Endometritis in the Pathogenesis of Perimenopausal Bleeding

**Sakna NAES[1]* and Howeidy II[2]**

[1]Department of Obstetrics and Gynecology, Ain Shams University, Abbasyia, Egypt

[2]Department of Clinical Pathology and Microbiology, Ain Shams University, Egypt

***Corresponding author:** Noha Abd El-Sattar Sakna, Department of Obstetrics and Gynecology, Ain Shams University, Abbasyia, Egypt

**Received:** November 05, 2017; **Accepted:** December 04, 2017; **Published:** December 11, 2017

**Abstract**

**Objective:** The goal of this study is to evaluate the prevalence of Chlamydial endometritis in women with perimenopausal bleeding presented at Ain Shams University Maternity Hospital outpatient clinics.

**Design:** A cross-sectional study. Setting: Ain Shams Maternity University Hospital. Patients and methods: 150 consented women were divided into two equal groups of 75 women in each one. Intervention: patients admitted through the reception room or out-patient clinics (hospital department) and they scheduled for Pipelle endometrial samples. Group I saught medical advice because of peri-menopausal bleeding while group II were attending the hospital due to any other cause other than vaginal bleeding. Pipelle endometrial biopsy was taken and sent for detection of *Chlamydia trachomatis* by PCR. Results: In group I, 82 specimens were positive for Chlamydia and the other 68 specimens were negative for Chlamydia while in group II only 22 specimens were PCR positive for chlamydia. There was a statistical significant correlation between positive cases of C. endometritis and Abnormal Uterine Bleeding (AUB).

**Conclusion:** screening for *Chlamydia trachomatis* in patients with perimenopausal bleeding is recommended.

**Keywords:** *Chlamydia trachomatis*; Menorrhagia

## Introduction

Abnormal Uterine Bleeding (AUB) in peri-menopausal age group is a common but ill-defined entity which needs proper evaluation. Goldstein et al [1] has defined AUB as "Patients having either metrorrhagia defined as vaginal bleeding separated from expected menses or menorrhagia defined as patients' subjective complaints of either increased duration or increased volume of flow or both". In general, women present themselves to the gynecologists whenever there is a departure from their personal menstrual experiences. Variations from the normal cyclical pattern in the peri-menopausal age may be due to physiological hormonal changes on one hand or may be due to neoplastic changes either benign or malignant, on the other hand. Therefore, accurate diagnosis of the causative factor of AUB in this age group is of utmost importance so that appropriate management can be established. Tests have evolved over the years starting from blind Dilatation & Curettage (D&C), to latest immune histo chemical markers [2].

Endometritis presents clinically by elevated temperature, uterine tenderness, vaginal bleeding, leukocytosis, or positive endometrial cultures. Clinically evident endometritis is usually presented in the setting of acute PID or postpartum or post abortive [3]. Due to its subtle clinical picture, the true incidence of this pathology among women is unclear, with estimates ranging from 0.8% to19.0%. 72% of histologic samples gathered from women asking care in STD clinics, were positive [4].

*Chlamydia trachomatis (C. trachomatis)* is the most frequent sexually transmitted bacterium [5]. Lower genital tract infection by this organism is usually asymptomatic in men and women, 50-66% of such infections in women remain undiscovered and consequently untreated, and leading to undesired long-term effects, ectopic pregnancy and tubal infertility are outstanding examples [6]. Hence, screening is needed to detect and manage this infection to decrease the period of infectivity, transmissibility and future adverse effects [7].

As culture techniques are hard to standardize, technically exhausting and not cheap, other tests have been arised [8]. Nucleic Acid Amplification Techniques (NAAT) are now being utilized to diagnose chlamydial infections. NAATs are used with noninvasively gathered samples, such as First-Void Urine samples (FVU) from men or women and vaginal smears leading to increased compliance of *C. Trachomatis* screening programs among asymptomatic persons [9].

In a Cochrane review, the mean prevalence of endometritis was 7% after elective cesarean section and 30% after nonelective or emergency cesarean section [10]. CE is characterized by plasma cell infiltration in the endometrium [11]. Most of the time CE is accidentally discovered after an endometrial biopsy or a Dilatation and Curettage (D&C) for different indications such as abnormal vaginal bleeding , postmenopausal bleeding , endometrial polyps , etc.

Accurate estimates of incidence data for Chlamydial infection of the female genital system using sensitive and specific methods like nucleic acid amplification tests are lacking in developing countries as Egypt. Few available data describe an increased incidence of infection, especially among symptomatic Egyptian women [12]. There is an ongoing debate as to whether or not screening of all women with menorrhagia and management of those diagnosed to be infected




**Citation:** Sakna NAES and Howeidy II. The Role of Chlamydial Endometritis in the Pathogenesis of Perimenopausal Bleeding. Austin J Obstet Gynecol. 2017; 4(4): 1084.

is needed or cost effective. The goal of this study is to evaluate the prevalence of Chlamydial endometritis in women with menorrhagia and answer the question to screen or not to screen.

## Patients and Methods

This was a cross-sectional study performed in A in Shams Maternity University Hospital involving 150 women; a first group 75 cases with perimenopausal bleeding and a control group of 75 perimenopausal women with normal menstruation attending gynecologic outpatient clinic (hospital department), for any reason other than bleeding. Pipelle endometrial biopsies were collected and sent for detection of *Chlamydia trachomatis* by PCR. This study was carried out in the period from January 2014 to December 2015 and it was approved by Ethical Committee of the Faculty of Medicine, Ain Shams University. Explanation of the procedure and verbal consent was taken for every patient.

### Inclusion criteria

1. Perimenopausal females; age 40-50 years.
2. Complain of dysfunctional uterine bleeding.
3. No gross uterine lesions were detected by vaginal US.
4. Women who live in Cairo

### Exclusion criteria

1. Patients who are immediately post partum or post abortion or known cases of sexually transmitted diseases.
2. Patients with any uterine abnormality detected by transvaginal sonar or hysteroscopy.
3. Patients with suspicion of pregnancy or malignancy.
4. Women who live outside Cairo.

### All patients were subjected to

1) Full history taking, complete physical examination.
2) Counseling and verbal consent was taken for every patient.
3) Pipelle endometrial biopsies were taken and sent to confirm *Chlamydia trachomatis* endometritis by PCR.

### Endometrial biopsy

**Transport medium:** 2-sucrose phosphate buffer (PH 7.0) supplemented with 5% fetal bovine serum, 50ug of streptomycin/ml, 100ug of vancomycin per ml and 12.5ug of amphotericin B (Fungizone) per ml (Phosphate Buffer Saline).

### Detection of the *C. Trachomatis* DNA in the collected specimens by

**Extraction of DNA:** This was performed using the QI Amp DNA mini kit (QIAGEN GmbH, Hilden, Germany Cat. No.51304) as described by the manufacturer.

**Real-time PCR assay:** According to Jaton and her colleagues, A forward primer Ctr_F (5′-CATGAAAACTCGTTCCGAAATAGAA-3′), a reverse primer Ctr_R (5′-TCAGAGCTTTACCTAACAACGCATA-3′) (which amplify a 71 bp DNA segment of C. trachomatis) and a minor-groove binder probe labeled with 5′FAM (6-carboxyfluorescein) Ctr_P (5′-TCGCATGCAAGATATCGA-3′) were selected. The Melting Temperature (Tm) of the probe was chosen to be 10-11°C higher than that of the corresponding primers. The reactions were performed in a final volume of 20µl, including 0.2µM each primer, 0.1µM Ctr_P probe, 10µl 2x Taq Man Universal Master Mix (Applied Bio systems) and 5µl DNA sample. Cycling conditions were 2 min at 50°C, 10 min at 95°C, followed by 45 cycles of 15s at 95°C and 1min at 60°C. Amplification and PCR product detection were performed with the One Step Sequence Detection system (Applied Biosystems) [13].

Each run included the testing of the positive and negative extraction control lysates, Tris-EDTA buffer in four reactions (no-template controls), and diethyl-pyrocarbonate-treated water (QIAGEN Germany) in duplicate reactions (negative reagent controls). The no-template controls and negative reagent controls were used to detect any nonspecific fluorescent signal or carry-over

**Table 1**: Clinic-demographic data of the population under study.

| | Group I | Group II | P- value |
|---|---|---|---|
| Age | 46.7 ± 4.8 | 46.3 ± 3.9 | > 0.05 |
| Body mass index (kg/m$^2$) | 31.4 ± 3.6 | 32.1 ± 3.1 | > 0.05 |
| Previous gravidity | 4 ± 1.2 | 3.8 ± 1.4 | > 0.05 |
| Previous parity | 3.2 ± 0.3 | 3 ± 0.1 | > 0.05 |
| Duration of marriage | 23.8 ± 2.8 | 24.3 ± 2.5 | > 0.05 |
| Frequency of coitus per week | 3.1 ± 0.4 | 2.9 ± 0.2 | > 0.05 |
| Mode of delivery | | | |
| Vaginal | 52 | 49 | > 0.05 |
| Cesarean | 23 | 26 | |
| Education | | | |
| ≤High school | 27 | 23 | > 0.05 |
| >High school | 48 | 55 | |
| Occupation | | | > 0.05 |
| House wife | 61 | 59 | |
| Employed/business | 14 | 16 | |
| Woman | | | |
| Previous use of IUCD | 59 | 52 | > 0.05 |
| Previous use of hormonal contraception | 62 | 65 | > 0.05 |

**Table 2**: Number and percent of positive cases for *C. trachomatis* by PCR.

| | Group I | Group II | P value |
|---|---|---|---|
| Positive cases | 44 (58.7 %) | 17 (22.7 %) | < 0.05 |
| Negative cases | 31 (41.3 %) | 58 (77.3 %) | (significant) |

**Table 3**: Correlation between age and presence of Chlamydia in the two groups with no significant correlation.

| Age (years) | PCR of Chlamydia | | | | | |
|---|---|---|---|---|---|---|
| | Negative | | Positive | | Total | |
| | No. | % | No. | % | No. | % |
| 40 - 45 y | 42 | 28 | 29 | 19 | 71 | 47 |
| 45 – 50 y | 47 | 31 | 32 | 21 | 79 | 53 |
| Total | 89 | 59 | 61 | 41 | 150 | 100 |
| P-value | > 0.05 | | | | | |

**Table 4**: Correlation between parity and presence of Chlamydia in the patients with no significant correlation.

| Parity | PCR of Chlamydia | | | | | |
|---|---|---|---|---|---|---|
| | Negative | | Positive | | Total | |
| | No. | % | No. | % | No. | % |
| 3-Jan | 45 | 30 | 30 | 20 | 75 | 50 |
| 4 or more | 44 | 29 | 31 | 21 | 75 | 50 |
| Total | 89 | 59 | 61 | 41 | 150 | 100 |
| P-value | > 0.05 | | | | | |

**Table 5**: Correlation between the form of abnormal uterine bleeding (AUB) and presence of Chlamydia in the patients with no significant correlation.

| Uterine bleeding | PCR of Chlamydia | | | | | |
|---|---|---|---|---|---|---|
| | Negative | | Positive | | Total | |
| | No. | % | No. | % | No. | % |
| Regular | 39 | 26 | 27 | 18 | 66 | 44 |
| Irregular | 50 | 33 | 34 | 33 | 84 | 66 |
| Total | 89 | 59 | 61 | 41 | 150 | 100 |
| P-value | > 0.05 | | | | | |

contamination. Run acceptability required obtaining the expected results from each control. Samples were considered positive if the amplification plots (i.e., change in normalized reporter signal versus PCR cycle number) from duplicate reactions showed definite exponential increase in fluorescent signal. If the fluorescent signal did not increase within 45 cycles, the sample was considered negative.

Statistical methodology: Retrieved data were recorded on an investigative report form. The data were analyzed with SPSS® for Windows®, version 15.0 (SPSS, Inc, USA). Description of quantitative (numerical) variables was performed in form of mean, Standard Deviation (SD) and range. Description of qualitative (categorical) data was performed in the form of numbers and percent. Analysis of numerical variables was performed by using student's unpaired t-test (for two groups) or ANOVA (for more than two groups). Analysis of categorical data was performed by using Fischer's exact test and Chi-squared test. Significance level was set at 0.05.

## Results

This cross sectional study involved 150 women consented to participate in this study; group I (test group) of 75 cases with perimenopausal bleeding and group II (control group) of 75 perimenopausal women with normal menstruation recruited from gynecologic outpatient clinic (hospital department), and complaining from any reason other than bleeding. Pipelle endometrial biopsies were collected and sent for detection of *Chlamydia trachomatis* by PCR. Both groups were comparable in terms of age, body mass index, gravidity, parity, duration of marriage, frequency of coitus per week, mode of delivery (vaginal or cesarean), level of education (≤High school or >High school), occupation (house wife or employed/ business woman) and previous use of IUCD or hormonal methods and (Table 1-4).

The 150 specimens were sent for detection of *Chlamydia trachomatis* by PCR. In group I, 44 (58.7%) specimens were positive for Chlamydia and the other 31 (41.3%) specimens were negative for

**Table 6**: Correlation between history of abortion and presence of Chlamydia in the patients with no significant correlation.

| History of abortion | PCR of Chlamydia | | | | | |
|---|---|---|---|---|---|---|
| | Negative | | Positive | | Total | |
| | No. | % | No. | % | No. | % |
| Positive | 40 | 27 | 32 | 21 | 72 | 48 |
| Negative | 49 | 33 | 29 | 19 | 78 | 52 |
| Total | 89 | 59 | 61 | 41 | 150 | 100 |
| P-value | > 0.05 | | | | | |

**Table 7**: Correlation between infertility and presence of Chlamydia in the patients with no statistical significant correlation.

| Infertility | PCR of Chlamydia | | | | | |
|---|---|---|---|---|---|---|
| | Negative | | Positive | | Total | |
| | No. | % | No. | % | No. | % |
| Fertile | 52 | 35 | 32 | 21 | 84 | 56 |
| Primary | 23 | 15 | 19 | 13 | 42 | 28 |
| Secondary | 14 | 9.3 | 10 | 6.7 | 24 | 16 |
| Total | 89 | 59 | 61 | 41 | 150 | 100 |
| P-value | > 0.05 | | | | | |

**Table 8**: Correlation between duration of marriage and presence of Chlamydia in the patients with no statistical significant correlation.

| | PCR of Chlamydia | | P-value |
|---|---|---|---|
| | Negative | Positive | |
| | Mean ± SD | Mean ± SD | |
| Duration of marriage | 24.9 ± 8.43 | 25.80 ± 8.19 | > 0.05 |

Chlamydia while in group II only 17 (22.7%) specimens were PCR positive for chlamydia. There was a significant difference between the two groups as regards the incidence of *C. trachomatis* among symptomatic perimenopausal women complaining of dysfunctional uterine bleeding (Table 4-8).

There was no statistically significant correlation between the presence of chlamydial endometritis and the age of participants, parity, form of bleeding, history of abortion, type of infertility and duration of marriage.

## Discussion

The goal of *Chlamydia Trachomatis* screening programs is to limit the morbidities from upper genital tract effects and the incidence of the infection by controlling its spread [14]. Moreover, pre-existing silent disease can spread more when patients undergo uterine instrumentation for further assessment and management of their problems. So, the Royal College of Obstetricians and Gynecologists advise that all patients undergoing uterine instrumentation should be screened for Chlamydia or should receive prophylactic antibiotics [15].

In Egypt and most Arab nations, the incidence of sexually transmitted diseases in general and Chlamydial genital infection in particular is not exactly known, reflecting the deficient specific diagnosis and management protocols. Different small studies from various countries showed different prevalences of *C. Trachomatis*

infection; United Arab Emirates (2.6%) [16], Jordan (3.9%) [17], Qatar (5.3%) [18], Saudi Arabia (15%) [19]. This difference in prevalence is linked to age of the individuals under study, as well as the different specific techniques utilized for diagnosis.

Chronic Endometritis (CE) is a subtle pathology which is hard to both diagnose and manage [20,21]. Chronic endometritis is usually clinically asymptomatic, but may be associated wild mild complaints including chronic pelvic pain, abnormal uterine bleeding, painful coitus and leucorrhea [22]. The presence of an inflammatory infiltration containing plasma cells is usually pathognomonic to chronic endometritis. Hence, it cannot be excluded an endometritis if, besides infiltration, there are factors such as attacking behavior against endometrial glands, the presence of an exudates inside gland lumina or the formation of granulomas [23].

The purpose of this study was to determine the prevalence of *C. trachomatis* in endometrial tissues of patients with perimenopausal bleeding. The use of PCR technology is the most currently accepted method for diagnosing endometrial tissue for *C. trachomatis* antigen and has been validated [24,25]. Nucleic acid amplification has a high sensitivity (90-97%) and specificity (99%). The samples are suitable for testing several days after collection, even if kept at room temperature [26-28]. Actually, Ain Shams University Teaching Hospital is one of the biggest referral hospitals in Egypt and manages women with any obstetric or gynecological complaint from a large geographical area so the rates were nonetheless striking.

In the current study, the *C. trachomatis* infection was detected in 44 cases (58.7%) in patients with perimenopausal bleeding and 31 cases (41.3%) were negative for chlamydia. In a similar study, that included 2,190 diagnostic hysteroscopies, histologic diagnosis of CE was made in 388 cases, it is found that several bacteria can cause CE, the most common among them *E. coli*, Streptococci, Staphylococci, Enterococcus fecalis, and Yeast species. *C. trachomatis* and Ureaplasma urealyticum were isolated in only a small proportion of the patients with a histologic diagnosis of CE in this study. Regarding the type of infectious agent, it is worthy underlining that at the endometrial level the most frequent agents found were common bacteria, accounting for about 60% of Cases; U. urealyticum was detected in 10% of cases. Unexpectedly, Chlamydia was demonstrated in only 2.7% of positive endometrial cultures. No cases of N. gonorrhea were found; this in partial agreement with the currnet study (13.3% of cases) [28].

At the endometrial level, the prevalence of *C. trachomatis* in our study was higher that reported in the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) study as reported that Chlamydia represents about 14% of women with chronic endometritis [29].

Some studies put no set of histologic features or degree of intensity of inflammation predicted a particular clinical presentation, a response by the clinician to prescribe antibiotics or outcome [30-32]. Also in another study implied that histological examination of an endometrial biopsy is a reproducible method for diagnosis and treatment of CE in asymptomatic patients prior to IVF/ICSI is substantial [33]. Moreover, in patients treated with antibiotics for C. trachamatis, the histological features of endometritis promptly resolves and endometrial cultures become negative [34].

In the current study there was no statistically significant correlation between the incidence of *C. trachomatis* and the age of participants, parity, form of bleeding, history of abortion, type of infertility and duration of marriage. Another study found that Chlamydial endometritis increases as age and parity increase, which was explained due to exposure to infections. This is in partial agreement with our study which found that CE increases with parity while here was no relation with age [35].

It is stated that there was an association of CE and salpingitis. It seems that CE is a marker of an ascending infection, which in younger patients might impair fertility by the presence of salpingitis. A genital tract infection that remains untreated or partially treated or a subclinical ascending infection may progress to cause CE and possible salpingitis with potential impact on fertility [36,37]. This was in accordance with findings from [38] who found in 45% of cases some pathological finding at diagnostic hysteroscopy prior to IVF most of these abnormalities were endometritis.

Bayer-garner [39] implied that CE was diagnosed in between 3% and 10% of women who complaining of abnormal uterine bleeding, also implied that CE was more common in women who experiencing dysfunctional uterine bleeding. Also, Krettek [40] found that *C. trachomatis* represent 3:5 fold in patients with abnormal uterine bleeding associated CE. This was in contrast with Wiesenfeld [24] study who found no relation between CE and abnormal uterine bleeding but these findings were limited to sample size and association between *C. trachomatis* and CE.

In one of the first studies on CE, reported that the clinical presentation of patients with CE was some types of vaginal bleeding [12]. Wiesenfeld reported that, the prevalence of CE was higher in women undergoing hysteroscopy due to abnormal uterine bleeding (14.4% vs 11.7%), furthermore, the indications related to bleeding [pre-menopausal abnormal uterine bleeding (AUB), suspected endometrial polyp, endocervical polyp, intracavitary myoma] they were present in up to 36.3% of cases of CE [24]. There was partial agreement with results of the current study and some studies [41,42], clinical reviews who using PCR to detect *C. trachomatis* in cases of CE. These studies proved that *C. trachomatis* was associated with severe CE and dysfunctional uterine bleeding is a common symptom of CE.

## Conclusion & Recommendations

In view of such findings, the aim of the present work was to detect the prevalence of *C. trachomatis* in symptomatic women complaining of perimenopausal bleeding. The current study documented higher than expected C trachomatis prevalence in these patients reflecting lack of STI-specific programs in Egypt. Review of these data led to a change of perimenopausal workup policy in our unit, with the introduction of Chlamydia serological screening and antibiotic treatment of positive cases. We hope to use the results of this study to help design and complete larger clinical trials involving the use of endometrial curettings for the detection of Chlamydial antigen by DNA amplification. This may lead to improved identification and characterization of this subgroup of women whose menstrual abnormalities are currently unexplained.

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