September 2010 | VOLUME 3 No.3 | Quarterly Publication



Journal Watch Summaries of recent topical publications in the medical literature Full Article pg 2



Test Announcement Tests now available in the clinical laboratory Full Article



Research & Development Endometritis Continued pg 7

The Laboratorian SM

Clinical Aspects of Endometritis

Author: Shlomo Stemmer, MD.

Endometritis is defined as an infection of the endometrium. It may be called endomyometritis when the infection extends also to the myometrium. Extension of the infection to the parametrial tissues (parametritis) may result in pelvic inflammatory disease (PID). Endometritis is divided into two: obstetric (most commonly post partum endometritis) and non-obstetric. Pathologists classify endometritis as acute or chronic. Acute endometritis is characterized by the presence of neutrophils within the endometrial glands. Chronic endometritis is characterized by the presence of plasma cells or lymphocytes in the endometrial stroma. The incidence of endometritis after a vaginal delivery is 1% to 3% and can be as high as 13% to 50% after a Caesarean section, depending on whether antibiotic prophylaxis was given prior to or during the surgery (1, 2).

Continued.....

Endometritis Author: Caitlin Moore

Femeris Women's Health Research Center

Endometritis is the inflammation of the endometrium or uterine lining, caused by both pregnancy and non-pregnancy related causes. In the non-obstetric population endometritis is further classified as acute or chronic. Both acute and chronic forms of endometritis have been associated with pelvic inflammatory disease (PID) and its associated pathogens - Neisseria gonorrhoeae and Chlamydia trachomatis. Broad spectrum antibiotics have proven to be an effective means for treatment of endometritis in additional to surgical procedures. However, if left untreated serious consequences may result including: infertility, ectopic pregnancy, recurrent PID, sepsis, or death (1).

Puerperal Endometritis

Puerperal endometritis occurs after childbirth and is the most common complication of delivery. Infections tend to be polymicrobial and typically result from the ascension of normal flora bacteria from the vaginal or GI tract. The most common pathogenic organisms associated with postpartum endometritis include Gram-positive cocci such as group B streptococcus and Staphylococcus epidermidis, Gram-negative bacteria such as Gardnerella vaginalis, Escherichia coli, Klebsiella pneumoniae, and Proteus mirabilis, and finally, anaerobes such as Peptostreptococcus species (1, 2, 3).

Incidence of infection is largely influenced by mode of delivery as well as patient's characteristics/risk factors. Rate of infection associated with vaginal deliveries is only 1% to 3%. Scheduled Caesarean deliveries completed before the onset of labor has an associated rate of 5% to 15%, whereas the rates associated with unscheduled Caesarean deliveries range from 15% to 20%. Risk factors shown to increase the incidence rate of puerperal endometritis include prolonged rupture of the membranes, prolonged labor, multiple vaginal examinations and internal monitoring during labor, bacterial vaginosis, young maternal age, and low socioeconomic status (1, 3).

Various clinical manifestations of puerperal endometritis have been identified including fever, lower abdominal pain, abnormal vaginal discharge/bleeding, abdominal distention, and malaise. Symptoms usually appear within 5 days of delivery. Diagnosis is based on clinical evaluation and exclusion of other sources of infection. Upon physical examination the following signs of infection may be observed: fever, lower abdominal pain, enlargement of the uterus, tachycardia, leukocytosis, and uterine tenderness (1, 3). Continued.....pg 7

WHAT'S INSIDE

P2	Journal	Watch
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- P3 Endometriosis
- New Test Announcements P4
- P5 Recent Publications
- P5 e-Quiz

- P5 QA Q&A
- P6 **Clinical Aspects of Endometritis**
- P7 Endometritis
- P8 Classifieds / Ads

UPCOMING EVENTS

10/2	FCMA: Florida Council of Nurse Midwives Statewide Continuing Education Meeting & Gala St. Augustine, FL	
10/8	WHS: Billings Clinic Women's Health Symposium Billings, MT	
10/8-10	ACOG: American Congress of Obstetricians & Gynecologists District I Annual Bar Harbor, ME	
10/8-10	ACOG: American Congress of Obstetricians & Gynecologists Annual District Meeting (Districts III, & VI) Key Biscayne, FL	
10/10-12	University of New Mexico (UNM) will host the combined Annual Meeting of the Southwest College Health Association (SWCHA) and the Rocky Mountain College Health Association (RMCHA) Albuquerque, NM	
10/17-20	ACOG: American Congress of Obstetricians & Gynecologists Armed Forces District Annual Meeting San Antonio, TX	
10/21-24	NASPGHAN: North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Annual Meeting New Orleans, LA	
11/20	ACOG: American Congress of Obstetricians & Gynecologists Minneapolis Section Annual Meeting	

Minneapolis, MN

Journal Watch

Haggerty CL, Hillier SL, Bass DC, Ness RB. 2004. Bacterial Vaginosis and Anaerobic Bacteria Are Associated with Endometritis. *Clin Infect Dis.* **39**:990-5.

Pelvic Inflammatory Disease (PID) is associated with the presence of Chlamydia trachomatis and/or Neisseria gonorrhoeae in one-third to one-half of cases. The remaining 50% to 70% of cases are associated with other microbes. This study examines the independent association of bacterial vaginosis and bacterial vaginosis- associated organisms in endometritis. When 278 women were studied, the frequency of microorganisms from the endometrium of women diagnosed with PID was determined. Of those women studied, 61% of women had growth of facultative or anaerobic bacteria in the endometrium. An increase in diphtheroids, black-pigmented Gram-negative rods, and anaerobic Gram-positive cocci was observed. Of those women studied, 54% were diagnosed with bacterial vaginosis by Gram stain and 90% of cases showed a depletion of H₂O₂-producing Lactobacillis species. These associations remain following exclusion of women with endometrial C. trachomatis and/or N. gonorrhoeae infection. This report suggests that vaginal microorganisms found in women with bacterial vaginosis ascend to the endometrium and cause upper genital tract infection. Previous studies by this group as well as another report that nongonococcal endometritis is more likely to result in reproductive morbidity than gonococcal endometritis. Therefore, it suggests treatment of all PID cases should include metronidazole since frequent isolation of bacterial vaginosis-associated organisms was found.

Ross JD, Brown L, Saunders P, Alexander S. 2009. *Mycoplasma genitalium* in asymptomatic patients: implications for screening. *Sex Transm Infect.* **85(6)**:436-7.

Mycoplasma genitalium, a small parasitic bacteria, was first isolated in 1980 from urethral specimens of male patients with non-gonococcal urethritis. Today this organism is widely recognized as a cause of urethritis in addition to being associated with cervicitis, endometritis, and pelvic infection. However, due to low rates of infection and effective treatment with antibiotics, screening the general population for M. genitalium is not necessary. Whether asymptomatic patients should be tested routinely remains to be determined. In this study, researchers monitor the prevalence of M. genitalium infectivity in asymptomatic males and females attending a sexual health clinic in the United Kingdom. Patients of interest were identified using a paper-based questionnaire and subsequently contacted to participate in the study. Genital Swabs and urine (both self-taken and physician-taken) were used for testing. Methods involved two separate PCR assays (MgPa and Mg219) which employed the use of different primer sets. Of the 308 patients tested, 292 of them (94.8%) were negative on both PCRs. Fourteen individuals (4.5%) tested positive in both reactions and 2 patients (0.6%) were positive on only the MgPa PCR. Furthermore, no significant associations were identified between M. genitalium infections

and age, gender, ethnicity or isolation site. While the rate of infection found here is low, only 4.5%, it is comparable to that of *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, both of which are screened for in asymptomatic individuals. Over the same time period, within the same population, the positivity rate of chlamydia was 9.8% and that of gonorrhea was only 3.4%. The researches conclude that this study provides support of the need for further analysis of the role and importance of *M. genitalium* screening in asymptomatic patients. Before such screening is recommended and implemented, further investigation regarding the risks and consequences of untreated infections is necessary; along with the development of a commercially available, inexpensive diagnostic assay.

Ettore C, Raffaele T, Achiropita L, Vincenzo P, Mariarosa F, Leonardo R. 2010. Correspondence between hysteroscopic and histologic findings in women with chronic endometritis. *Acta Obstetricia et Gynecologica*. **89**:1061–1065.

Chronic endometritis (CE) in most of the cases is asymptomatic and difficult to diagnose. Common symptoms associated with CE are a) spotting b) mild and undefined pelvic pain c) leukorrhea and d) vaginal bleeding in most patients. Since pelvic examination and transvaginal sonography do not help in diagnosis of CE, the authors rely on the technique of "fluid hysteroscopy" to characterize the presence of red endometrium scattered throughout the cavity referred to as "strawberry aspects". The authors have previously utilized fluid hysteroscopy for diagnosis of CE with 93.4% accuracy and described the various signs associated with diagnosis. In the present study the authors aim to correlate the fluid hysteroscopy diagnosis of CE with severity of inflammation at histology for grading. In this study, 211 women previously diagnosed for CE were subjected to mini-hysteroscopy along with 30 women with no sign of endometrial inflammation as a control group. The severity of inflammation was scored as grade 0 (no inflammation) to grade 2 (moderate/severe inflammation). Similarly endometrial samples were collected from all of the 211 CE positive patients along with the control group for histological examination and graded for severity of inflammation based on the identification of a) superficial stromal edema b) increased stromal densisty c) pleomorphic stromal inflammatory infiltrate dominated by lymphocytes and plasma cells. Of the 211 women, 200 (94.8%) diagnosis of CE confirmed with that of histological examination. Out of 211 women 149 of them exhibited grade 2 severity of inflammation, while 51 of them had the grade 1 form. Moreover a significant correlation was observed between the grade 1 and 2 histological examination and that of hysteroscopic grading. Furthermore the statistical analysis was found to be significant in comparison with the control group indicating the concordance between hysteroscopy and histology in the case of grade 2 compared to grade 1 inflammation. The result of the study has demonstrated a good correlation between hysteroscopic and histological evaluation of severity of inflammation in CE.

Endometriosis Author: Eli Mordechai, Ph.D.



Endometriosis is a condition that occurs when the tissue lining the uterus (endometrium), begins to grow outside of the uterus. It is a leading cause of pelvic pain and one of the major reasons for laparscopic surgery and hysterectomy in the United States. This condition usually occurs in women of childbearing age and is problematic for this age group due to its association with infertility. While the exact etiology of endometriosis remains unknown, studies have revealed the condition is exacerbated by the hormone estrogen. As women progress through menopause, symptoms begin to abate and will ultimately resolve.

Diagnosis of endometriosis has proven difficult. It has been estimated that over one million women within the United States are affected, with the reported ranges between 3% and 18% of the female population. With this in mind, endometriosis should be suspected when an individual presents with any of the following complaints:

- Pain before and during periods
- Pain during intercourse
- Pain upon urination
- · Painful bowel movements
- Gastrointestinal issues, including diarrhea, constipation and nausea
- Problems conceiving

Unfortunately, determining the exact prevalence of this condition has been made more difficult due to the fact that approximately 20% to 25% of affected individuals will have no overt symptomologies and, as a result, remain untreated until fertility issues arise. It has been estimated that 20% to 50% of women seeking treatment for fertility issues, and as many as 80% of women with chronic pelvic pain, are actually suffering from endometriosis. Often times there are no cues indicating endometriosis aside from the general pelvic pain and discomfort reported by the patient. In some instances confirmation can be obtained in the form of nodules occurring behind the uterus and along the ligaments that attach it to the pelvic wall upon rectovaginal examination. While these nodules and the presence of pain allude to a case of endometriosis, they are not conclusive. Diagnostic evaluation, often by ultrasound, aids in the confirmation process but, again, is not conclusive. These non-invasive methods are employed to aid in ruling out other pelvic diseases with common symptomologies but, again, are not definitive. Direct visual inspection of the pelvis and abdomen, combined with biopsy of the overgrown tissue are

required for accurate diagnoses. Laparoscopic methods have been employed as a means to decrease the invasiveness of this diagnosis. The procedure, typically performed on an outpatient basis, is carried out under general anesthesia. Biopsies are obtained and analyzed for the presence of endometriosic tissue implants as well as for the exclusion of malignancies that could mimic endometriosis symptomatically.

There is no cure for endometriosis but multiple treatment options exist for the management of pain and to address fertility issues. Factors that are considered when deciding the proper method include consideration of the woman's needs and expectations, particularly her desire to have children, along with her symptomology and age. Pain management is often addressed with hormone therapy aimed at reducing estrogen levels, which should decrease the size of the endometrial implants and, in turn, decrease pain levels. Often this is achieved by prescribing common birth control hormones or with non-steroidal anti-inflammatories. In instances where a woman wishes to conceive a child, treatment is a little more complicated and is often addressed through infertility treatment, surgery, or a combination of the two. Surgical strategies are aimed at restoring the pelvic anatomy to as close to its normal arrangement as possible. In mild to moderate cases of endometriosis surgery can be performed laparscopically to keep it minimally invasive while more severe cases require a more extensive and invasive surgery. Hysterectomy is an absolute last resort reserved for women who do not respond to any of the milder forms of treatment or who have very severe symptoms.

Identification of biomarkers specific for endometriosis would not only alleviate the need for surgical evaluation but would also allow for more routine screening of individuals, particularly those women suffering from infertility.

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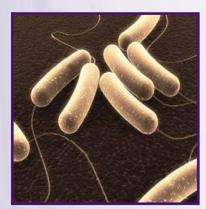
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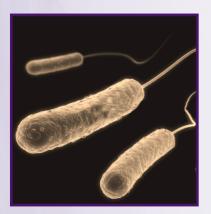


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- 154 *Enterococcus faecium* by Real-Time PCR (Reflex to vancomycinresistant Van A & Van B by Real-Time PCR)
- 168 Enteropathogenic *Escherichia coli* (O157:H7) by Real-Time PCR
- 274 Human Rotavirus A by Real-Time PCR
- 158 Listeria monocytogenes by Real-Time PCR
- 272 Norwalk Virus by Real-Time PCR
- 160 Salmonella by Real-Time PCR
- 161 Shigella spp. by Real-Time PCR



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RECENT PUBLICATIONS =



MEDICAL DIAGNOSTIC LABORATORIES, L.L.C. (MDL)

Abstracts

 Villasmil ML, Ansbach A, Nickels, Jr., JT. 2010. The putative lipid transporter, Arv1, is required for activating pheromoneinduced MAP kinase signaling in *Saccharomyces cerevisiae*. Yeast Genetics and Molecular Biology Meeting, Vancouver, British Columbia, Canada. July 27 – August 1, 2010.

Peer-Reviewed Papers

- Peña KC, Adelson ME, Mordechai E, Blaho JA. 2010. Genital herpes simplex virus type 1 in women: Detection in cervicovaginal specimens from gynecological practices in the United States. J *Clin Microbiol.*. 48(1): 150-153.
- 2. Blaho, JA. 2010. Oncoapoptosis: A novel molecular therapeutic for cancer treatment. *IUBMB Life*. 62(2): 87-91.
- Ingvarsdottir K, Blaho JA. 2010. Association of the herpes virus major tegument structural protein VP22 with chromatin. *BBA Mol Basis Dis*, 1799(3-4): 200-206.
- Biggs C, Walsh P, Overmyer CL, Gonzalez D, Feola M, Mordechai E, Adelson ME, Iacono, KT. 2010. Performance of influenza rapid antigen testing in influenza in emergency department patients. *Emerg Med J.* 27(1): 5-7.



Peer-Reviewed Papers

 Gallagher G, Megjugorac NJ, Yu RY, Eskdale J, Gallagher GE, Siegel R, and Tollar E. The lambda interferons: guardians of the immune epithelial interface and the Th2 response. J Interferon Cytokine Res. 30(8): 306-15.



- 1. **True or False:** Endometriosis and Endometritis are both associated with an infectious process.
- 2. What is the incidence of endometritis in unscheduled cesarean deliveries?
 - a. 1% to 3% b. 5% to 15%
- c. 15% to 20% d. 20% to 35%
- 3. **True or False:** If left untreated, endometritis may result serious consequences including infertility, ectopic pregnancy, recurrent PID, sepsis, or death.
- 4. **True or False:** When treating endometritis, the antibiotic regimen should include coverage of Gram-positive and Gram-negative bacteria.
- 5. Endometritis can be associated with the following pathogens:
 - a. Chlamydia trachomatis & Neisseria gonorrhoeae
 - b. Peptostreptococcus species & Group B Strep
 - c. Gardnerella vaginalis
 - d. All of the above

For results to the electronic Epidemiology Quiz, please visit <u>www.mdlab.com</u> and click on the e-Quiz link.



Q: Recently, I have noticed that my office keeps receiving specimen discrepancy notices to verify the date of specimen collection. Why are we receiving these and how can we prevent them in the future so that it does not affect the turnaround time for our results?

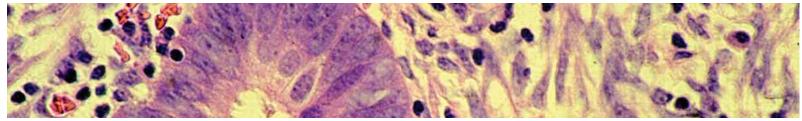
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 - A future date
 - Incorrect year

To prevent such discrepancies,

- ✓ Be sure that the test requisition form is completed on the same day the specimen is collected.
- ✓ Compare the information written on the vial with the information written on the test requisition form to ensure accuracy.
- \checkmark Double check the date of collection to make sure that dates are not transposed, recorded incorrectly, etc.

If you have a question you would like addressed in future issues, please email your question(s) to QAQ&A@mdlab.com



Clinical Aspects of Endometritis

Continued from......pg

Causes and risk factors

Endometritis usually results from an ascending infection from the cervico-vaginal flora (3). Common pathogens isolated are *Chlamydia trachomatis, Neisseria gonorrhoeae, Ureaplasma urealyticum, Peptostreptococcus* species, *Gardnerella vaginalis, Bacteroides bivius,* and Group B Streptococcus. In certain populations it has been associated with tuberculosis. Acute endometritis is commonly caused by an infection with *Staphylococcus aureus* and *Streptococcus* species following an instrumental procedure. Postpartum endometritis is frequently a polymicrobial infection involving aerobes and anaerobes that attach to the decidua and proliferate. Caesarean section delivery is a major risk factor for endometritis. Other risk factors include prolonged rupture of the membranes, preterm labor, chorioamnionitis, prolonged labor with frequent vaginal exams and low socioeconomic status.

Diagnosis

Patients with endometritis present with fever, lower abdominal or pelvic pain, general malaise, abnormal vaginal bleeding or discharge. In the obstetric patient, a foul-smelling lochia may be present. Patients with PID often complain of dysuria and/ or dysparunia. Physical exam may reveal a distended and tender lower abdomen. Bowel sounds may be decreased. Pelvic exam may show vaginal discharge, cervix, uterine, and adnexal tenderness. Laboratory tests include complete blood count although, the finding of leukocytosis is difficult to interpret due to the physiologic leukocytosis of pregnancy (up to 20,000). Wet prep, blood cultures and cervicovaginal DNA sampling for associated pathogens such as Chlamydia trachomatis, Neisseria gonorrhoeae and other organisms, should be obtained. Urinalysis and urine cultures are helpful for differential diagnosis. Endometrial biopsy may aid in the evaluation of a non-obstetric patients with suspected chronic endometritis. The endometrial tissue is sent for microbiologic and histologic studies. The presence of plasma cells is diagnostic for chronic endometritis. Imaging studies are usually reserved for patients that do not respond to antibiotic therapy. Pelvic ultrasound is rarely needed, however, they may be helpful for excluding retained products of conception, pelvic hematoma, or the presence of an unknown foreign body such as a forgotten IUD. Abdominal and pelvic CT scans may be needed to rule out septic pelvic thrombophlebitis in patients not responding to adequate antibiotic therapy after 48 hours. Laparoscopy is rarely performed unless other conditions such as appendicitis are suspected. Other conditions to be considered in the differential diagnosis are pyelonephritis, urinary tract infection, and viral syndrome.

Treatment

Parenteral antibiotic therapy is the mainstay treatment for endometritis (4). For mild cases of endometritis following a vaginal delivery, oral antibiotics may be an appropriate treatment. The antibiotic regimen should include coverage of Gram-positive and Gram-negative bacteria. A combination of I.V. clindamycin and gentamicin is commonly used. Another popular regimen is the use of a second or third-generation cephalosporin such as cefoxitin or cefotetan plus doxycycline. For severe cases of acute endometritis, triple antibiotic therapy using ampicillin, gentamicin, and metronidazole provide coverage against most pathogens involved in serious pelvic infections. Endometritis complicated by PID and a tubo-ovarian abscess (TOA) may require surgical intervention if no clinical improvement is present after 48-72 hours of combination I.V. antibiotic therapy. Drainage of a thick wall abscess using laparoscopy or by intervention radiology followed by triple antibiotic therapy, is sometimes needed to treat this possible life threatening infection. A hysterectomy with bilateral salpingooophorectomy is rarely performed to treat end-stage PID with pyosalpinx or TOA.

Prognosis

Severe endometritis may result in secondary infertility. Endometrial curettage for retained products of conception or for postpartum hemorrhage may cause intrauterine synechiae. Endometritis complicated by PID may involve the fallopian tube and lead to salpingitis. Once the fallopian tube becomes damaged; the patient will be at risk for future ectopic pregnancy and infertility. Prophylactic antibiotic therapy use during cesarean section (5), early diagnosis of endometritis, and the use of combination antibiotic therapy for treatment will prevent most short and long term complications.

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In most cases, broad-spectrum antibiotics administered orally are adequate for treatment of infection. However, intravenous antibiotics, particularly clindamycin in combination with gentamicin, have also been used to treat puerperal endometritis. Once the appropriate treatment is administered, improvement is typically observed within 48-72 hours. While treatment at the onset of infection remains effective, recent studies have examined the benefits of preoperative, prophylactic antibiotic administration. The observed 53% decrease in postpartum endometritis in the context of the use of prophylactic antibiotics, provides strong support for the implementation of such practices (1).

Acute Endometritis vs. Chronic Endometritis

Acute endometritis is characterized by inflammation associated with the presence of microabscesses or neutrophils within the endometrial glands. Often this form of infection is preceded by PID caused by an invasive gynecologic procedure or sexually transmitted disease such as gonorrhea or chlamydia (4). In recent years, studies examining the etiology of endometritis have identified an association between bacterial vaginosis (BV) and anaerobic bacteria. In 2004, Haggerty and colleagues examined the correlation of N. gonorrhoeae, C. trachomatis, bacterial vaginosis, anaerobic bacteria, facultative bacteria and lactobacilli with endometritis, among 278 infected patients using cultures and histological methods. More than 50% of patients with endometritis were classified as having bacterial vaginosis determined by a vaginal Gram stain. Acute endometritis was also associated with diphtheroids, black-pigmented Gram-negative rods, and anaerobic Gram-positive cocci. Furthermore, a negative association was identified between endometritis and the presence of hydrogen-peroxide producing lactobacillus, which prevents pathogen overgrowth and maintains the normal vaginal flora. These results suggest that bacteria associated with bacterial vaginosis ascend to the endometrium and establish an infection. Accordingly, researchers suggest the addition of metronidazole to treatment plans for coverage against anaerobic and BV-associated organisms (5).

Chronic Endometritis is characterized by inflammation specifically associated with a high number of plasma cells located in the endometrial stroma. Additional features distinguishing this condition from acute cases are superficial mucosal stromal edema, stromal breakdown, and spindle cell alteration of the stroma (6). A number of causes have been identified including past clinical or surgical procedures, intrauterine devices, submucosal leiomyoma, polyps, PID, and the presents of common bacteria. Any cause of chronic irritation to the endometrium has the potential to result in a chronic inflammatory reaction (7). Symptoms for both acute and chronic endometritis are the same as those listed above for

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puerperal endometritis; for example, abnormal vaginal bleeding and lower abdominal pain. One exception does apply; fever is more commonly observed in acute cases (4). In contrast to the treatment of postpartum and acute endometritis, antibiotic therapies are rarely employed as remedies for chronic endometritis. Rather, treatment of chronic endometritis involves surgical ablation, curettage, or a hysterectomy (7).

In a study by Smith and colleagues, aimed at reviewing the clinical data of chronic endometritis cases and assessing samples for specific histopathologic features, various degrees of inflammation were observed. However, the level of inflammation did not appear to impact the symptoms of infection in type, duration, or severity (7). Another study, by Hagerty, Smith and Bocklage, cites direct correlations between incidence of chronic cases and age. The highest percentage of cases (41.1%) was seen in women between 41-50 years of age. Increased incidence was observed in perimenopausal women as well. Furthermore, the use of hormones and number of pregnancies was found to be associated with chronic endometritis (6).

While many studies have paved the way for our current understanding of endometritis, the etiology, clinical manifestations and treatment options, and additional research will be of great value in further examining the implications of this infection, improving diagnostics, and addressing those questions left unanswered.

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Research & Development

Endometritis Continued ... pa 7

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.... pg 4

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