Miliary and Vesicular Lesions - WCE 2017

POSTER SUMMARY

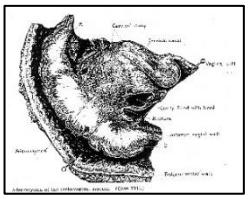
Are miliary and vesicular lesions classical?
Dan C. Martin, MD
Ronald E. Batt, MD, PhD (1933-2017)

There is research in the rheumatologic literature that is not paralleled in the gynecologic literature that. Recent rheumatologic approaches to *Chlamydia*-induced reactive arthritis include not only the types of diagnostic testing, but also antibiotics combinations. (Carter 2010, Carter 2017) This suggests a need for additional gynecologic research.

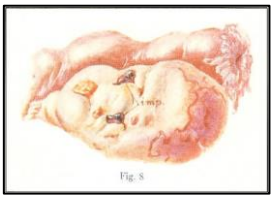
Clinicians can anticipate that 1.4% to 18% of their patients with pelvic pain, but no salpingitis or adhesions will have chlamydia (Schliep 2016, Taylor-Robinson 2009) and up to 64% with adhesions. But, we do not know if how many having laparoscopy for endometriosis will have peritoneal chlamydia or other agents.

Some clear and red, subtle miliary lesions suggestive of endometriosis have been inflammatory. (Martin 1994, Martin 1995, Marsh 2005, Cabana 2010) This suggests a research or clinical need to clarify the role of bacteria including chlamydia, mycoplasma, mycobacteria including tuberculous, viruses, spirochetes, talc, douching and other inflammatory agents in these cases.

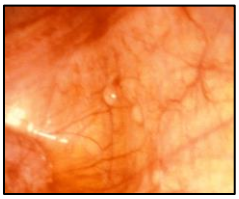
This need is reinforced by the suggestions for future research from the 2011 and 2014 World Congresses of Endometriosis. Study of the microbiome of the reproductive tract and/or the gut in women with or without endometriosis is needed. (Rogers et al. 2013, Rogers, et al. 2017) Sampson 1940) Colorless, amenorrheic lesions were described in 1950



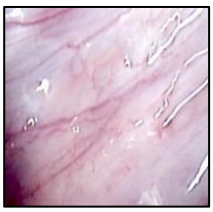
Cullen 1917



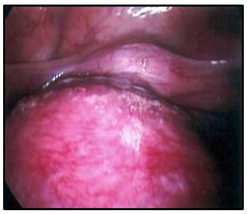
Sampson 1924



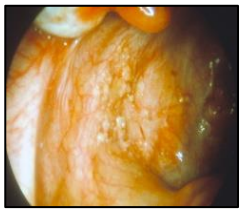
Amenorrheic Endometriosis 1990



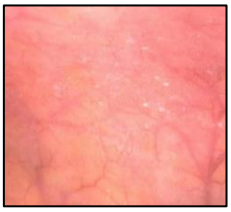
Granulation Tissue - Cabana 2010



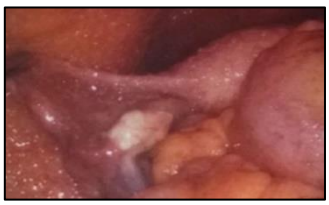
Borderline Malignancy in Martin files



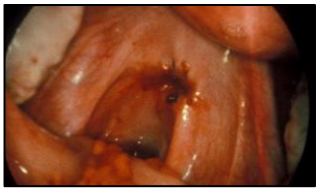
Psammoma Bodies in Martin files



Peritoneal carcinomatosis – Jung 2015



Tuberculosis - Swe 2016



Coexistent deep endometriosis & chlamydia – Martin 1990

The coexistent deep endometriosis & chlamydia are on page 22 of the 1991 Laparoscopic Appearance of Endometriosis Color Atlas, Second Edition.
(Martin 1991) That publication is a free PDF download at:
http://www.danmartinmd.com/files/coloratlas1990.pdf.

Clinical Conclusions

- Develop a screening questionnaire to cover history of:
  - ❑ Childhood maltreatment including emotional neglect, physical neglect, emotional abuse, physical abuse, and sexual abuse
  - ❑ Condylomata, ulcerative vulvitis, chlamydia, human papilloma virus, genital herpes, trichomonas, and pelvic inflammatory disease.
- Prepare for confidentiality issues.
- Anticipate childhood maltreatment in 78% of women with chronic pelvic pain and 65% of healthy women.
- Anticipate childhood emotional neglect in 58% of women with chronic pelvic pain and 42% of healthy women.
- Anticipate a history of sexual abuse in 12% to 43% of patients with chronic pelvic pain and up to 21% of healthy women. Some of those occurred in childhood.
- Anticipate that women with chronic pelvic pain and adhesions will have an increased chance of a history of physical abuse.
- Screen for major and minor depression.
- Anticipate a 1.4% to 18% prevalence of chlamydia in patients with chronic pelvic pain in the absence of salpingitis or adhesions and up to 64% prevalence with acute or sub-acute pain and adhesions.
- Do urinary NAA testing for chlamydia and other STDs as part of initial evaluation, with worsening o symptoms and as part of routine follow-up.
- Anticipate a lower prevalence of human papilloma virus, genital herpes, trichomonas, pelvic inflammatory disease, condylomata, syphilis and tuberculosis.
- Approach miliary and other subtle lesions as possibly inflammatory or malignant. Do peritoneal NAA testing for chlamydia and other STDs. Authorize use of NAA for peritoneal specimens with your lab.
  See CDC / MMWR information on non-approved use of NAA testing:
  https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6302a1.htm#Box4 in
  https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6302a1.htm
- Consider adhesions as possibly inflammatory.
- Do urinary, endometrial, peritoneal testing for C trachomatis, GC, trichomonas and other indicated diseases.
- Do focused biopsies or excision.
- Consider frozen section to determine need for cancer staging or tuberculosis testing.
- Consider iron stains with brown peritoneal discoloration.
- Notify pathologist of the size of lesions, particularly those of 1 mm or less.
- Believe pathologists if they make a diagnosis. If pathologists give you “no specific findings” or a similar description, that is not a diagnosis. Ask for the specimens to be cut again.
- Inflammatory pathology is not endometriosis, but may predispose to the development of endometriosis.

Research Conclusions

- Document your clinical considerations and protocols in your papers.
- Consider serum, urine, endometrial, tubal or peritoneal cultures, NAA, PCR, immunologic, histology or other testing.
- Consider collagen / muscle stains of histologic specimens.
- Consider iron stains of histologic specimens.
- Consider testing for C trachomatis, C pneumoniae, other chlamydias, human papilloma virus, other viruses, genital herpes, M. genitalium, M. hominis, Ureaplasma spp, nontuberculous mycobacteria, talc, and other diseases that may be relevant in research.
- Expand the use of STARD criteria to endometriosis research.

REFERENCES

ACOG 2011 childhood sexual abuse
ACOG Committee opinion number 498: Adult manifestations of childhood sexual abuse.
Obstet Gynecol. 2011 Aug;118(2 Pt 1):392-5
DOI: 10.1097/AOG.0b013e31822c994d
PMID: 21775872 [Indexed for MEDLINE]
Studies on chronic pelvic pain, sexual abuse, other forms of abuse and a possible relationship with endometriosis and sexually transmitted diseases have changed over time. The 2011 *ACOG report Committee opinion number 498: Adult manifestations of childhood sexual abuse*, does not mention endometriosis or sexually transmitted diseases (STD), but notes sexual abuse in 12–40% of children. (ACOG 2011) A more recent study reported that childhood emotional neglect was frequently (58.4%) reported by women with chronic pelvic pain than other forms of childhood maltreatment including physical and sexual abuse. However, sexual abuse was noted in 29.9% of endometriosis patients and 20.8% of healthy controls. (Poli-Neto 2017) A 2016 study noted no increased risk of endometriosis with either a history of sexual or physical abuse. That study reported 39% of women reporting physical abuse and 43% sexual abuse. A history of chlamydia was found in 10.4% with sexual abuse, 13% with physical abuse, 2.6% with no sexual abuse and 1.4 % with no physical abuse. Similar trends, with lower prevalence, were noted for human papilloma virus, genital herpes, trichomonas, pelvic inflammatory disease and condylomata. A history of physical abuse, versus no history, was associated with a higher risk of adhesions (aRR: 2.39). (Schliep 2016)
With sexual abuse reported in 12% to 43% and chlamydia in 1.4% to 13% of women with chronic pelvic pain, STD testing appears indicated in clinical care and mandatory in research of chronic pelvic pain and associated diseases such as endometriosis. At a theoretical level, this id even more indicated in those with documented pelvic inflammation.

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As-Sanie 2014 abuse & chronic pain
As-Sanie S, Clevenger LA, Geisser ME, Williams DA, Roth RS
History of abuse and its relationship to pain experience and depression in women with chronic pelvic pain.
Am J Obstet Gynecol. 2014 Apr;210(4):317.e1-8.
DOI: 10.1016/j.ajog.2013.12.048
PMCID: PMC4086742
PMID: 24412745 [Indexed for MEDLINE]
Epub 2014 Jan 8.
Adolescent or adult sexual abuse was associated with greater pain-related disability. A history of physical abuse or sexual abuse appears to hold a stronger relationship with current depressive symptoms than pain experience for women with CPP

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Batt 2014 retrocervical septum
Ronald E. Batt, Dan C. Martin, and Kunle Odunsi
Endometriosis of the retrocervical septum is proposed to replace the anatomically incorrect term endometriosis of the rectovaginal septum
Human Reproduction, Vol.29, No.12 pp. 2603–2605, 2014
doi:10.1093/humrep/deu279
We propose that the term retrocervical septum be added to the medical lexicon to designate the anatomic location of endometriosis of the septum that separates the vagina and posterior vaginal fornix from the rectovaginal pouch of Douglas. Use of the terms retrocervical septum and endometriosis of the retrocervical septum would correct the century-long misuse of the

anatomically incorrect term, endometriosis of the rectovaginal septum.The term endometriosis of the retrocervical septum is meant to designate endometriosis of the septum that separates the vagina and posterior vaginal fornix from the rectovaginal pouch of Douglas. So defined, endometriosis of the retrocervical septum describes the anatomic location of the adenomyomas illustrated in the publications of Cullen (Cullen, 1919; Cullen, 1920) and the anatomic location of DIE described by Vercellini et al. and Chapron et al. (Vercellini et al., 2000; Chapron et al., 2002). (DCM: Kononckx 1988)Importantly, as Chapron et al. emphasized, precise anatomic details are not only essential for understanding the pathogenesis of DIE, but knowledge of the precise location also provides the basis for selecting the optimal operative procedure for complete excision of the DIE lesions (Chapron et al., 2004). In that scientific context, we propose that the term retrocervical septum be added to the medical lexicon to designate the anatomic location of endometriosis of the septum that separates the vagina and posterior vaginal fornix from the rectovaginal pouch of Douglas.
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Bienenfeld 2016 screening depression.
Bienenfeld D. Screening Tests for Depression
http://emedicine.medscape.com/article/1859039-overview
Jan 27, 2016
The estimated prevalence of depressive disorders is 13-22% in primary care clinics but is only recognized in approximately 50% of cases.
Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up.
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Cabana 2010 granulation tissue
Cabana MD, Foster-Barber AE, Hong T, Martin DC, Shenkin B. Teen troubled by a trembling leg. Contemporary Pediatrics. 27(6):22-27, 2010
Clear blebs - nonspecific granulation tissue consistent with endometriosis

Carter 2010 PCR and RT-PCR for chlamydia
J. D. Carter, L. R. Espinoza, R. D. Inman, K. B. Sneed, L. R. Ricca, F. B. Vasey, J. Valeriano, J. A. Stanich, C. Oszust, H. C. Gerard, and A. P. Hudson. Combination antibiotics as a treatment for chronic chlamydia-induced reactive arthritis a double-blind, placebo-controlled, prospective trial. Arthritis & rheumatism 62 (5, May):1298–1307, 2010
DOI 10.1002/art.27394

Carter 2017 PCR and RT-PCR for chlamydia
John D. Carter & Alan P. Hudson (2017) Recent advances and future directions in understanding and treating Chlamydia-induced reactive arthritis, Expert Review of Clinical Immunology, 13:3, 197-206, DOI: 10.1080/1744666X.2017.1233816
Many reports indicate that a significant portion of patients diagnosed with undifferentiated inflammatory arthritis are PCR positive for DNA from C. trachomatis in the synovium ([35]; JDC, APH unpublished observations).
We point out that PCR and RT-PCR data demonstrating chlamydiae in synovial tissue are not at all unique to patients with Chlamydia-induced ReA. Several reports have described similar findings in a small percentage of patients with other arthritides, including osteoarthritis and even normal controls [36–38]. Such background PCR-positivity rates have ranged from 5% in normal controls [37] to as high as 20%[38]. These observations have called into question the pathologic importance of PCR and RT-PCR findings in patients with Chlamydia-induced ReA. However, the prevalence of identifying chlamydial nucleic acids in synovial tissue samples from patients with conditions other than ReA is significantly lower than that of finding them in similar samples

from patients with Chlamydia-induced ReA. One recent study reported that the rate of PCR positivity in synovial tissue from patients with suspected Chlamydia-induced ReA (62%) is significantly higher than that found in synovial tissue from subjects with OA (12%; p-value <0.0001) [33].The large difference in the prevalence of PCR positivity for chlamydiae in Chlamydia-induced ReA compared to control populations highlights the importance of host genetic variability, host tolerance, and important potential arthritogenic differences of the various chlamydial serovars (see below).
The primary etiologic agent for post-venereal ReA is the bacterium *Chlamydia trachomatis*; its respiratory relative, *C pneumoniae*, has also been implicated in disease induction although to a lesser degree.
C. trachomatis appears to be responsible for eliciting as much as 50% of all cases of ReA, pulmonary infection with *C. pneumoniae*, which is far more common, is responsible for less than 15% of cases.
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Darville 2013 Pelvic Inflammatory Disease Workshop
Darville T; Pelvic Inflammatory Disease Workshop Proceedings Committee.
Sex Transm Dis. 2013 Oct;40(10):761-7.
DOI: 10.1097/OLQ.0000000000000028
PMID: 24275724 [Indexed for MEDLINE]
In November 2011, the National Institutes of Health convened a workshop of basic researchers, epidemiologists, and clinical experts in pelvic inflammatory disease to identify research gaps hindering advances in diagnosis, treatment, and prevention. This article summarizes the presentations, discussions, and conclusions of this group and highlights significant controversies that reveal aspects of pelvic inflammatory disease research that would most greatly benefit from the application of newer molecular, immunologic, and radiologic techniques. Multiple limitations to performing new clinical trials exist; however, emerging data from ongoing clinical trials will add to the current body of knowledge regarding prevention and treatment strategies. In addition, use of established health care databases could serve as a valuable tool for performance of unbiased epidemiologic outcome studies.
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Fallon 1950 amenorrheic lesions
Fallon J, Brosnan JT, Manning JJ, Moran WG, Meyers J, Fletcher ME: Endometriosis: A report of 400 cases. Rhode Island Med J 1950; 18:15-23.
Describes colorless, amenorrheic lesions
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Fortenberry 2017 adolescent STDs
Fortenberry, J Dennis. Sexually transmitted infections: Overview of issues specific to adolescents. UpToDate accessed 5/5/17
A recent review of STD testing in adolescents in UpToDate notes physical and sexual violence from dating partners reported by as many as 20 percent of adolescent girls. The review includes concerns for techniques of exam, techniques of exams and unique issues in adolescents. Those unique issues include confidentially, self-consent laws, STD reporting laws, "age of consent" laws, pregnancy, and notifications of partners.
DCM Note: STD testing is suggested for protocols of pelvic pain evaluation and management. Surgical evidence of inflammation suggests the need for additional testing. Although miliary lesions are most commonly endometriosis, they have also been inflammatory. It appears prudent to do nucleic acid amplification testing (NAAT) of those peritoneal lesions at surgery and are needed in research protocols.
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Gaitán 2002 diagnosing PID
Gaitán H, Angel E, Diaz R, Parada A, Sanchez L, Vargas C.
Accuracy of five different diagnostic techniques in mild-to-moderate pelvic inflammatory disease. Infect Dis Obstet Gynecol. 2002;10(4):171-80.
DOI: 10.1155/S1064744902000194
PMCID: PMC1784624
PMID: 12648310 [Indexed for MEDLINE]
Clinical criteria represent the best diagnostic method for discriminating PID. Laparoscopy showed the best specificity and is thus useful in those cases having an atypical clinical course for discarding abdominal pain when caused by another factor. The other diagnostic methods might have limited use.
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Goldstein 1980 atypical petechial-like and blebs
Goldstein DP, De Cholnoky C, Emans SJ. Adolescent endometriosis. J Adol Health Care. 1980;1:37-41.
Goldstein, et al. Endometriosis was encountered in 66 of 140 patients (47%) who underwent laparoscopy for chronic pelvic pain. Pelvic pain associated with this diagnosis was both cyclic and acyclic and typically began 2.9 years after menarche. The youngest patient with proved endometriosis was 10.5 years. Uterine anomalies were found in 8 patients with endometriosis and 4 without. Three patients (5%) had extensive disease of the peritoneum, ovaries and tubes as well as involvement of adjacent structures (stage IV). Nine patients (14%) had implants on the bladder and/or rectum. The 7 patients (11%) with fixed retroversion all had stage II or IV disease. In 13 patients (20%) with stage I disease, the lesions encountered were quite atypical, consisting of petechial-like areas on the pelvic peritoneum and uterosacral ligaments. One patient was found to have a cluster of bleblike areas on the serosa of the anterior uterine wall. Microscopically these proved to be endometrial implants. The close-up view of the pelvic peritoneum afforded by a laparoscopy is a decisive advantage over the "naked eye," which fails to distinguish the subtle early implant.
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Goodwin 1984 the tomato effect
Goodwin, James S; Goodwin, Jean M. The tomato effect. Rejection of highly efficacious therapies. JAMA, 251: 2387-2390, 1984
The tomato effect in medicine occurs when an efficacious treatment for a certain disease is ignored or rejected because it does not make sense in the light of accepted theories of disease mechanisms and treatment of these diseases.
The tomato effect interferes with the acceptance and use of useful remedies.
Questions to Ask
Before we accept a treatment, we should ask "Is this a placebo?"
Before we reject a treatment, we should ask "Is this a tomato?"
The only 3 issues that matter in picking a therapy:
Does it help?
How toxic is it?
How much does it cost?
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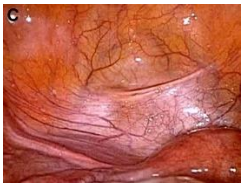
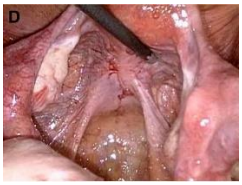
Jang 2014 nontuberculous mycobacterial
Jang HY, Burbelo PD, Chae YS, Kim T, Cho Y, Park HT. Nontuberculous mycobacterial infection in a clinical presentation of Fitz-Hugh-Curtis syndrome: a case report with multigene diagnostic approach. BMC Womens Health. 2014 Aug 12;14:95.

DOI: 10.1186/1472-6874-14-95
PMCID: PMC4141662
PMID: 25115526 [Indexed for MEDLINE]
Fitz-Hugh-Curtis syndrome (FHCS) associated with nontuberculous mycobacteria (NTM).
DCM Note: Pictures look like tuberculosis, cancer, LMPT, psammoma bodies or endometriosis.





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Jung 2015 carcinomatosis mimicking tuberculosis
Jung EY, Hur YJ, Lee YJ, Han HS,Sang JH, Kim YS. Peritoneal carcinomatosis mimicking a peritoneal tuberculosis (Case Report). Obstet Gynecol Sci 2015;58(1):69-72
Peritoneal carcinoma is a rare disease with nonspecific symptoms.
Patients with peritoneal TB mimicking peritoneal carcinoma are common.
Case report of peritoneal carcinomatosis mimicking peritoneal TB.
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Marsh 2005 premenarcheal inflammatory lesions
Marsh and Laufer (Fertil Steril 83:758, 2005) suggests a need for testing. Although the authors concluded the lesion were endometriosis, Table 1 has inflammatory pathology in 4 and reactive in the 5th of 5 premenarcheal girls. Glands or stroma were only found in the postmenarcheal group. No specific STD testing was done.
DCM Note: This is in a population with an increased risk of childhood sexual abuse.
"lesions visibly consistent with endometriosis"
"standard medical and gastrointestinal evaluation..."
Five premenarcheal girls with chronic pelvic pain were identified who had been evaluated with a standard medical and gastrointestinal evaluation without definitive for an etiology for their pain. All subjects were identified as having clear, red, and/or white lesions consistent with stage I endometriosis based on the standard American Society for Reproductive Medicine Classification of Endometriosis (15). Identification of the lesions was facilitated by visualization under liquid media (16).
One could argue that these patients do not have endometriotic lesions given that their pathology revealed no glands. Given, however, the classic appearance of the endometriotic lesions, the subject's response to surgical and subsequent hormonal therapy, and the pathologic presence of hemosiderin and stroma (DCM???), these lesions can be classified as endometriosis or antecedents of endometriosis.
4 of 5 with granulation. 1 of 5 with reactive mesothelial hyperplasia
Fibroconnective tissue focally lined by mesothelium with multiple areas of granulation tissue on the surface, possibly representing early adhesions
Mesothelium-lined fibroconnective tissue of peritoneum and fragments of inflamed granulation tissue
Chronic inflammation with associated vascular proliferation and reactive mesothelial cells
Reactive mesothelial hyperplasia and psammomatous calcifications
Multiple focal areas of granulation tissue with lymphocytic infiltrates, no glandular structures identified
Theories
Proposed theories include retrograde menses (1, 2), hematologic or lymphatic spread (3), coelomic metaplasia (4), embryonic müllerian rests (5, 6), and immunologic abnormality (7).
Endometriosis is often seen in cases of women with obstructive anomalies of the reproductive

tract and tends to resolve once the obstruction is relieved (8, 9). Endometriosis is also noted to occur in young women with a positive family history for endometriosis, and thus a genetic etiology has also been proposed (10).
70% of adolescents who have pelvic pain that does not respond to medical therapy (11, 12). Since endometriosis is believed to be a progressive disease, its early diagnosis and treatment is particularly important in this population (13, 14).
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Martin 1990 & 1991 laparoscopic appearance slides and atlas
Laparoscopic Appearance of Endometriosis, Volume I (Slide Atlas), second edition. Martin DC (ed). Memphis; Resurge Press, 1990
Laparoscopic Appearance of Endometriosis, Color Atlas, second edition. Martin DC, et al (eds). Memphis; Resurge Press, 1991
Positive Chlamydia cultures associated with an inflammatory appearing endometriosis lesions were published in 1990 and are on page 22 of the 1991 Laparoscopic Appearance of Endometriosis Color Atlas. That is a free download at http://www.danmartinmd.com/files/coloratlas1990.pdf.
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Martin 1993 look-alike
Martin, D.C. and Jansen, R (1993). Look-alike lesions. In Martin, D.C. (ed.) Atlas of Endometriosis, pp. 16.1-16.6. (London: Gower (Mosby) Medical Publishers)
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Martin 1994 clear & opaque lesions
Martin DC, Khare VK and Parker L. Clear and opaque vesicles: endometriosis, psammoma bodies, endosalpingiosis or cancer? In Coutinho E, Spinola P, De Moura L, Hanson (eds): *Progress in the Management of Endometriosis*: The Pathenon Publishing Group, 1994, pp 129-132.
Although an attempt is made to distinguish psammoma bodies, endosalpingiosis and endometriosis, Ripps (1991) has documented a coexistence of positive anti-G. trachomatisIgG titers and endometriosis in 35% of patients with pain and/or infertility. See Ripps 1991. Furthermore, in the absence of malignant cells, the finding of psammoma bodies is not an indication for extirpative surgical therapy. In addition, the lack of association of positive cultures or direct fluorescent antibodies fails to suggest a need for antibiotic therapy in these patients.
"*The inclusion of anti-C trachomatis IgG titers, serological markers for other etiological agents of pelvic inflammation and observation for psammoma bodies appears to be prudent in research protocols in the study of endometriosis, infertility, pain and ovarian cancer*."
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Martin 1995 *C trachomatis* IgG associations
Martin, D C; Khare, V K; Miller, B E. Association of chlamydia trachomatis immunoglobulin gamma titers with dystrophic peritoneal calcification, psammoma bodies, adhesions, and hydrosalpinges. Fertil Steril 63: 39-44
Of the 58 patients who had cervical chlamydia culture or direct fluorescent antibody (28 with positive C. trachomatis IgG titers and 30 with negative C. trachomatis IgG titers), none (0%) had positive culture or direct fluorescent antibody.
10 with dystrophic calcification
  8 0f 8 with psammoma bodies had + CT IgG titers
  0 of 2 nonpsammomatous had + CT IgG titers
10 of 12 with hydrosalpinges had + CT IgG titers
3 of 3 with Fitx-Hugh-Curtis adhesion had + CT IgG titers

None (0 of 25) had a history of chlamydia,
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Martin 1997 age related *Chlamydia* titers
Dan C. Martin, Vivek K. Khare, Brigitte E. Miller, and Frances R. Batzer. Association of positive *Chlamydia trachomatis* and *Chlamydia pneumoniae* Immunoglobulin γ titers with increasing age. J Am Assoc Gynecol Laparosc 4(5):583-586, 1997
Chlamydia trachomatis IgG titers were positive in 15 (79%) of 19 of women with ovarian cancer, 9 (90%) of 10 age-matched controls, and 14 (67%) of 21 patients with infertility and pain. When analyzed by age, 4 (40%) of 10 patients under 30 years and 34 (85%) of 40 patients 30 years of age or older had positive titers (p = 0.007). Of 21 women with positive Chlamydia pneumoniae titers, 17 (81%) had positive C. trachomatis titers, and 17 (85%) of 20 with positive C. trachomatis titers had positive C. pneumoniae titers.
The test kit used in this study may not be adequate in older patients due to cross-reaction with C. pneumoniae titers. Further evaluation of C. trachomatis IgG titers as a marker in the study of ovarian cancer will require titers that are more specific than those we used. Although these titers may be useful as an immunologic screening marker in infertile patients, results should be interpreted with caution. A positive test may not be evidence of C. trachomatis infection and is not an indication for specific therapy. Successful use of some currently available C. trachomatis IgG titers in algorithms for infertility may be related to a patient's age.
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McCormack 1979 chlamydia persistence at 15 months
McCormack WM, Alpert S, McComb DE, Nichols RL, Semine DZ, Zinner SH. Fifteen-month follow-up study of women infected with Chlamydia trachomatis. N Engl J Med. 1979 Jan 18;300(3):123-5.
DOI: 10.1056/NEJM197901183000305
PMID: 758599 [Indexed for MEDLINE]
Brown University, State Laboratory Institute, Massachusetts Department of Public Health Channing Laboratory, Peter Bent Brigham Hospital, Harvard Medical School;
DCM Note: In the 1974-75 academic year, Brown University (?) did not treat positive (+) Chlamydia trachomatis cultures in 20 (4.6%) 0f 439 unselected women college students or positive (+) titers in 60 (13%) of 463 women. There was persistence without therapy in 50% (7 of 14%) on follow-up at 16 to 17 months.
DCM Note: Chlamydia trachomatis was reported as a cause of nongonococcal urethritis in 1975. (Holmes 1975) I was a chief resident in 1975-76 and shared administrative and clinical responsibility for treating the women who had been in an observational study at the Johns Hopkin Hospital that paralleled the one reported by McCormack in 1979 after Holmes's 1975 report of Chlamydia trachomatis associated with nongonococcal urethritis.
After many years during which they were of interest only to ophthalmologists and ornithologists, chlamydial infections recently have burst into general medical awareness.[1]
It has now been shown that this interesting intracellular parasite is a cause of nongonococcal urethritis,[2] *infantile pneurnonia*[3] *pelvic inflammatory disease*[4] *and epididymitis,*[5] *in addition to its long-established role in trachoma, lymphogranuloma venereum and inclusion conjunctivitis.*
C. trachomatis was isolated from 20 (4.6 per cent) of 439 women whose genital specimens were examined for this organism. Antibody to C. trachomatis was detected in the genital secretions of 60 (13 per cent) of 463 women, including all but two whose cultures contained C. trachomatis. Two (0.5 per cent) of these women were infected with Neisseria gonorrhoeae.
Eleven women had been treated in the 16 to 17 months follow-up interval.
Seven of the 14 women who did not report interim antimicrobial treatment were found to be infected 16 to 17 months.

Only one of the seven women whose genital specimens contained C. trachomatis during the follow-up examination had noted an abnormal vaginal discharge during the preceding month. The examiner noted a second participant to have an abnormal vaginal discharge. Examination of the other six infected women was normal.
The natural history of sexually acquired chlamydial infection in women has not been defined. *Convincing evidence is accumulating that C. trachomatis is a cause of pelvic inflammatory disease" although the risk that this complication will develop in an infected woman is unknown. Women who are identified as the source of nongonococcal urethritis or of neonatal chlamydial infection should be treated with tetracycline or erythromycin regardless of symptoms or findings on physical examination. The data presented here indicate that infection with C. trachomatis can persist for many months; some infected women may have neither symptoms nor signs of infection.*
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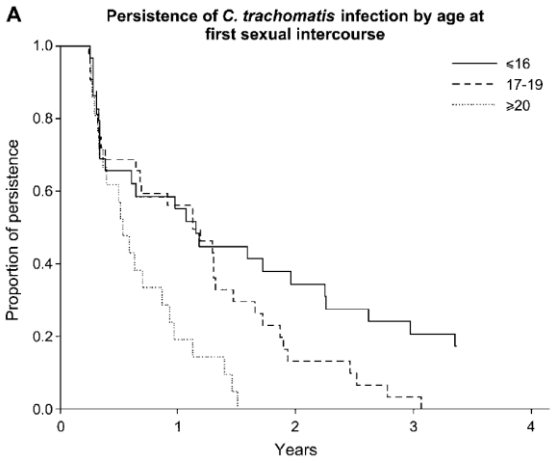
Molano 2014 6% chlamydia persistence at 4 years
Mónica Molano, Chris J. L. M. Meijer, Elisabete Weiderpass, Annie Arslan, Hector Posso, Silvia Franceschi, Margarita Ronderos, Nubia Munñoz, and Adriaan J. C. van den Brule. The natural course of Chlamydia trachomatis infection in asymptomatic Colombian women: A 5-year follow-up study. The Journal of Infectious Diseases 2005; 191:907–16.
1Department of Pathology, Vrije Universiteit Medical Center, Amsterdam, and 2Laboratory for Pathology and Medical Microbiology, PAMM
Institute, Eindhoven, The Netherlands; 3Unit of Field and Intervention Studies, International Agency for Research on Cancer, Lyon, France;
4Divisio´n de Investigacio´n, Instituto Nacional de Cancerologı´a, Bogota, Colombia
Approximately 70% of infections with *C. trachomatis* run an asymptomatic course that remains undetected and can result in severe complications, such as pelvic inflammatory disease, tubal infertility (6%– 21% of *Chlamydia*-infected women), pelvic pain (18%– 24% of *Chlamydia*-infected women), and ectopic pregnancy (7%–9% of those who become pregnant) [1, 2]. In addition, an epidemiological association between the presence of antibodies to *C. trachomatis* and cervical intraepithelial neoplasia (CIN) lesions has been observed [3–6], but its direct role in the development of cervical lesions is still unclear.
We studied *C. trachomatis* infection, as a risk factor for CIN, in a population-based cohort (a group of low-income women from Bogota, Colombia) study of the natural history of human papillomavirus (HPV) infection and the role that other risk factors play in CIN. Baseline data on *C. trachomatis* infection in this population show that the prevalence of *C. trachomatis* infection is 5.3% [13].
Approximately 46% of the infections were persistent at 1 year, 18% at 2 years, and 6% at 4 years of follow-up, as determined by use of plasmid PCR without any consideration for serotypes. In 94% of the women, *C. trachomatis* infections had cleared at 4 years of follow-up (figure 1). Rates of clearance were higher for women who had used oral contraceptives and for women who had their first sexual intercourse at ≥20 years of age



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MMWR 2014 laboratory recommendations

MMWR. Recommendations for the Laboratory-Based Detection of Chlamydia trachomatis and Neisseria gonorrhoeae – 2014. Recommendations and Report 63, Vol 2, March 14, pages 1-19, 2014.

https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6302a1.htm

Use for non-approved testing

https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6302a1.htm#Box4

Nucleic acid amplification tests (NAATs) that are cleared by the Food and Drug Administration (FDA) are recommended for detection of genital tract infections caused by Chlamydia trachomatis and Neisseria gonorrhoeae infections in men and women with and without symptoms. For detecting these infections of the genital tract, optimal specimen types for NAATs are vaginal swabs from women and first catch urine from men. (CDC 2014)

NAATs have not been cleared by FDA for the detection of peritoneal disease, but appear reasonable for extragenital infections based on increased sensitivity, ease of specimen transport and processing. Because these specimen types have not been cleared by FDA for use with NAATs, laboratories must establish performance specifications when using these specimens to meet Clinical Laboratory Improvement Amendments (CLIA) regulatory requirements and local or state regulations as applicable prior to reporting results for patient management. (CDC 2014)

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Nassar 2008 polymerase chain reaction, sterile pyuria.

Nassar FA, Abu-Elamreen FH, Shubair ME, Sharif FA.

Detection of Chlamydia trachomatis and Mycoplasma hominis, genitalium and Ureaplasma urealyticum by polymerase chain reaction in patients with sterile pyuria.

Adv Med Sci. 2008;53(1):80-6.

DOI: 10.2478/v10039-008-0020-1

PMID: 18614434 [Indexed for MEDLINE]

PCR testing of sterile pyuria showed a significant number of C. trachomatis, Mycoplasma, and Ureaplasma infections. Consequently, PCR is recommended for the detection of those microorganisms in the urine samples of sterile pyuria patients.

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NCCWCH 2013 fertility assessment

National Collaborating Centre for Women's and Children's Health. Fertility: assessment and treatment for people with fertility problems. February 2013

https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0068976/pdf/PubMedHealth_PMH0068976.pdf

A meta-analysis of 23 test evaluation studies found that the discriminative capacity of chlamydial antibody testing, using enzyme-linked immunosorbent assay (ELISA), immunofluorescence or microimmunofluorescence is comparable to that of HSG in the diagnosis of tubal pathology.380 [Evidence level 2b] Elevated titres of chlamydial antibodies in women were significantly associated with tubal disease.381 The titre of chlamydial antibodies has also been reported to be more accurate in predicting severe tubal pathology than unspecified tuboperitoneal abnormalities.382 However, it has been reported that the negative predictive value for pelvic pathology from the use of clinical features in addition to the chlamydial antibody titre is not significantly higher than that from the chlamydial antibody titre alone at 53%; this may not justify the avoidance of a diagnostic and confirmatory laparoscopy.383 [Evidence level 3]
A cohort study found that chlamydial antibody levels are quantitatively related to severity and extent of tubal pelvic damage. An elevated chlamydial antibody titre result is significantly associated with poor live birth rates, but not pregnancy rates.384 [Evidence level 2b] However, the chance of conception with or without tubal surgery is related to the degree of damage found at laparoscopy, with the chlamydial antibody titre adding no further diagnostic value.385 [Evidence level 2b]
Chlamydia trachomatis is present in 11% of the sexually active population aged 19 years or less.357 It is a major cause of pelvic inflammatory disease, leading to chronic abdominal pain, ectopic pregnancy and tubal factor infertility.358,359
The Chief Medical Officer's Expert Advisory Group on Chlamydia has called for action to reduce the prevalence and morbidity of chlamydial infection. It recommends that consideration be given to screening couples attending fertility clinics and women undergoing procedures requiring instrumentation of the uterus.365 [Evidence level 4]
DNA techniques such as polymerase chain reaction and ligase chain reaction for analysis of cervical and urine specimens are highly sensitive and specific for diagnosing chlamydial infection.366– 368 [Evidence level 2b]
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Peipert 1997 clinical and laparoscopic
Peipert JF, Boardman LA, Sung CJ.
Performance of clinical and laparoscopic criteria for the diagnosis of upper genital tract infection.
Infect Dis Obstet Gynecol. 1997;5(4):291-6.
DOI: 10.1155/S1064744997000501
PMCID: PMC2364552
PMID: 18476154
Commonly used minimal clinical criteria for pelvic inflammatory disease and the laparoscopic triad of tubal edema, erythema, and purulent exudate have limited sensitivity with correspondingly high false negative rates.
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Poli-Neto 2017 childhood maltreatment notes
Poli-Neto OB, Tawasha KA, Romão AP, Hisano MK, Moriyama A, Candido-Dos-Reis FJ, Rosa-E-Silva JC, Nogueira AA.
History of childhood maltreatment and symptoms of anxiety and depression in women with chronic pelvic pain.
J Psychosom Obstet Gynaecol. 2017 Mar 29:1-7.
Childhood emotional neglect was frequently (58.4%) reported by women with chronic pelvic pain than other forms of childhood maltreatment including physical and sexual abuse. However, sexual abuse was noted in 29.9% of endometriosis patients and 20.8% of healthy controls. (Poli-Neto 2017)

The estimated prevalence of reported childhood maltreatment was 77.9% for women with CPP and 64.9% for healthy women (p=0.07). Emotional neglect was more frequently reported by women with CPP than by healthy women (58.4% versus 41.5%, p = 0.04). The CPP patients were more frequently victims of multiple types of maltreatment (>4) than the healthy controls (18.2% versus 10.4%, p = 0.02).
The prevalence of the remaining forms of childhood maltreatment did not differ significantly from those observed in healthy women: physical neglect (58.4% versus 44.1%, p = 0.08), emotional abuse (48% versus 35.1%, p=0.10), physical abuse (45.4% versus 31.2%, p=0.07), and sexual abuse (29.9% versus 20.8%, p=0.19).
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Renz 2015 Fitz-Hugh-Curtis
Renz N(1), Baur M(2), Stickel F(3).
Right upper quadrant pain in a young female.
J Gastrointestin Liver Dis. 2015 Mar;24(1):10.
doi: 10.15403/jgld.2014.1121.nrz.
PMID: 25822427 [Indexed for MEDLINE]
34-year-old with 2 weeks right upper quadrant and lower quadrant abdominal pain. C-reactive protein (100 mg/l; upper limit of normal. + Chlamydia trachomatis DNA by polymerase chain reaction. Fitz-Hugh-Curtis at laparoscopy.
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Ripps 1991 *Chlamydia* trachomatis associations
Ripps BA, Martin DC. Focal pelvic tenderness, pelvic pain and dysmenorrhea in endometriosis. J Reprod Med Vol. 36 (7, July): 470-472 1991.
35% (16 of 45) of patients with endometriosis and 68% (13 of 19) of patients without endometriosis had positive *Chlamydia trachomatis* titers. These differences were statistically significant (P = .03)
59 patients with documented endometriosis
A positive titer was associated with endometriosis in 55% of the cases (16 of 29). If the *Chlamydia trachomatis* titer was negative, endometriosis was seen in 83% of the patients (29 of 35).
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Rogers 2013 Future Directions for Endometriosis Research:
Peter A. W. Rogers, Thomas M. D'Hooghe, Asgerally Fazleabas, Linda C. Giudice, Grant W. Montgomery, Felice Petraglia, and Robert N. Taylor. Defining Future Directions for Endometriosis Research: Workshop Report From the 2011 World Congress of Endometriosis in Montpellier, France
Reproductive Sciences 20(5): 483-499. 2013
DOI: 10.1177/1933719113477495
Clinical assessment of women with pelvic pain can be a poor indicator of disease seen at laparoscopy. (Taylor-Robinson 2012) In a study of pelvic inflammatory disease in 109 women, 22 at laparoscopy had salpingitis, 19 had adhesions without salpingitis, 20 had endometriosis or ovarian pathology, and 48 no observable abnormality. In all laparoscopic categories, Ureaplasma spp and *Mycoplasma hominis*, but not *Mycoplasma genitalium*, were at least as common in the cervix/vagina as *Chlamydia trachomatis* and equally frequent in the endometrium. The results reported for the whole group of women with pain highlight the difficulties in making a precise microbial diagnosis and highlight the need for further investigation into the links between the microbiome, pain, and endometriosis.
Recommendation. Metagenomic studies should be undertaken of the microbiome of the reproductive tract and/or the gut in women with or without endometriosis

(Taylor-Robinson 2012) Taylor-Robinson D, Jensen JS, Svenstrup H, Stacey CM. Difficulties experienced in defining the microbial cause of pelvic inflammatory disease. Int J STD AIDS. 2012;23(1):18-24
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Rogers 2017 Research Priorities for Endometriosis
Rogers PA, Adamson GD, Al-Jefout M, et al. WES/WERF Consortium for Research Priorities in Endometriosis. *Research Priorities for Endometriosis*. Reprod Sci. 2017 Feb;24(2):202-226.
The results reported for women with pain highlights the need for further investigation into the links between the microbiome, pain, and endometriosis.
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Sampson 1921 & 1940 appearance
Sampson JA: Perforating hemorrhagic (chocolate) cysts of the ovary. Their importance and especially their relation to pelvic adenomas of the endometrial type ("adenomyoma" of the uterus, rectovaginal septum, sigmoid, etc.). Arch Surg 1921; 3:245-323.
Sampson JA: The development of the implantation theory for the origin of peritoneal endometriosis. Am J Obstet Gynecol 1940; 40:549.
Sampson discussed appearances including cysts, blebs, red raspberries, purple raspberries and blueberries from 1921 to 1940. Illustrations of those appearances show lesions suggesting sizes in in millimeters.
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Sarli 2001 Fitz-Hugh Curtis syndrome
Sarli L(1), Villa F, Iusco DR.
The value of laparoscopy in the diagnosis and therapy of violin-string like perihepatic nonpostoperative adhesions.
Surg Endosc. 2001 Mar;15(3):323. Epub 2001 Mar 13.
DOI: 10.1007/s004640042010
PMID: 11344440 [Indexed for MEDLINE]
Institute of General Surgery and Surgical Therapy, Parma University School of Medicine, Via Gramsci 14, 43100 Parma, Italy. leosarli@ipruniv.cce.unipr.it
Three cases of Fitz-Hugh Curtis syndrome (FHCs) diagnosed laparoscopically with microbiological or serological evidence of chlamydia.
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Schliep 2016 Sexual and physical abuse
Schliep KC, Mumford SL, Johnstone EB, Peterson CM, Sharp HT, Stanford JB, Chen Z, Backonja U, Wallace ME, Buck Louis GM.
Sexual and physical abuse and gynecologic disorders.
Hum Reprod. 2016 Aug;31(8):1904-12. doi: 10.1093/humrep/dew153. Epub 2016 Jun 22.
Schliep, in a study of endometriosis and pain looking at a history of sexual or physical abuse, reported 39% of women reporting physical abuse and 43% sexual abuse. A history of chlamydia was found in 10.4% with sexual abuse, 13% with physical abuse, 2.6% with no sexual abuse and 1.4 % with no physical abuse. Similar trends, with lower prevalence, were noted for human papilloma virus, genital herpes, trichomonas, pelvic inflammatory disease and condylomata. A history of physical abuse, versus no history, was associated with a higher risk of adhesions.
No increased risk of endometriosis with either a history of sexual or physical abuse. However, hat study reported 39% of women reporting physical abuse and 43% sexual abuse. A history of chlamydia was found in 10.4% with sexual abuse, 13% with physical abuse, 2.6% with no sexual abuse and 1.4% with no physical abuse. Similar trends were noted for human papilloma virus, genital herpes, trichomonas, pelvic inflammatory disease and condylomata.

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Swe 2016 Tuberculosis Mimicking Malignancy
Thein Swe, Akari Thein Naing, Zaw Win Phyo and Malar Thwin
A Rare Presentation of Peritoneal Tuberculosis Mimicking Malignancy Journal of Investigative Medicine High Impact Case Reports
October-December 2016: 1–3
DOI: 10.1177/2324709616679191
63-year-old female with abdominal ascites and no malignancy on biopsy. High levels of serum cancer antigen and rheumatoid factor.
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Taylor-Robinson 2009 pelvic inflammatory disease
Taylor-Robinson D, Stacey CM, Jensen JS, Thomas BJ, Munday PE.
Further observations, mainly serological, on a cohort of women with or without pelvic inflammatory disease.
Int J STD AIDS. 2009 Oct;20(10):712-8.
Epub 2009 Sep 16.
DOI: 10.1258/ijsa.2008.008489
PMID: 19759049 [Indexed for MEDLINE]
100 women with lower abdominal pain
11 pre-op salpingitis
6 salpingitis at laparoscopy
17 pre-op probable salpingitis
6 salpingitis at laparoscopy
12 (43%) of 28 with pre-op probable or + salpingitis
56 pre-op unlikely to have salpingitis
5 salpingitis at laparoscopy
22 women salpingitis at laparoscopy
14 (64%) with GT IgG >or=1:128
18 women adhesions
12 with GT IgG >or=1:128
49 with no abnormalities
9 (18%) with GT IgG >or=1:128

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Taylor-Robinson 2012 pelvic inflammatory disease
Taylor-Robinson D, Jensen JS, Svenstrup H, Stacey CM.
Difficulties experienced in defining the microbial cause of pelvic inflammatory disease.
Int J STD AIDS. 2012 Jan;23(1):18-24.
DOI: 10.1258/ijsa.2011.011066
PMID: 22362682 [Indexed for MEDLINE]
Laparoscopy for PID in 109 women
22 (20%) salpingitis
19 (17%) adhesions without salpingitis
20 (18%) endometriosis or ovarian pathology
48 (43%) no observable abnormality
Ureaplasma spp. and Mycoplasma hominis, but not Mycoplasma genitalium, were at least as common in the cervix/vagina as Chlamydia trachomatis and equally frequent in the endometrium.

Of 28 women who had C. trachomatis organisms in the vagina/cervix, 13 had them in a Fallopian tube (ratio 2.2:1); the ratio was 6:1 for Neisseria gonorrhoeae, 8:1 for M. genitalium, 21:1 for M. hominis and 31:1 for Ureaplasma spp. M. hominis organisms in a large number were detected most often in women with salpingitis.
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