PREVENTION OF INFERTILITY SOURCE DOCUMENT

PREVENTION OF SALPINGITIS BY A CHLAMYDIA ERADICATION CONTROL EFFORT BACKGROUND

Chlamydia trachomatis causes about 4 to 5 million infections annually in the U.S.[1] Since chlamydia became a reportable disease in the U.S. in 1986, the number of cases in both men and women have increased each year to current rates of 290/100,000 women and 52/100,000 men in 1995 [1]. The greater number of reported cases in women than men reflects more widespread screening for chlamydia in women than men and the increase in rates also probably reflect increased screening over this time.

The prevalence of chlamydia infection is highest for sexually active women aged 15-21 and declines thereafter. However, based upon serum antibody to chlamydia, women continue to become infected until about age 30 at which time the prevalence of chlamydial antibody plateaus at about 50%.

The prevalence of chlamydia infection has ranged widely from 3 to 5% in asymptomatic women to over 20% in women seen in sexually transmitted disease (STD) clinics [2]. Chlamydia causes well-defined symptomatic infections of the mucosal surfaces of the urethra, cervix, endometrium and fallopian tubes. However, most women with chlamydia have infections at these sites that produce non-specific symptoms or, commonly, no symptoms. It has been demonstrated repeatedly that sexually active populations where little diagnostic testing and specific treatment is being used, the prevalence of infection can reach very high levels because chlamydia is so often asymptomatic.

DIAGNOSIS OF CHLAMYDIA

Considerable advance has occurred in diagnostic tests for *C. trachomatis* in the past decade. The cell culture system and antigen detection systems have largely been replaced by automated methods to detect amplified *C. trachomatis* DNA or RNA. The two most widely used tests are the ligase chain reaction (LCR) and polymerase chain reaction (PCR). Both the LCR and PCR can be used on urine, cervical and urethral specimens. These tests detect 1 to 10 chlamydial elementary bodies compared to 10,000 for non-amplified enzyme immunoassay tests. LCR generally detects 15 to 40% more infections than culture. The performance of PCR appears better on urine than cervical specimens, owing to inhibitors in cervical mucus which may reduce the sensitivity up to 15% [3]. The specificity of LCR and PCR are over 99%.

Serologic testing in not useful to identify active chlamydial infection. The baseline prevalence of antibody in sexually active populations is high, often 50% or greater. In most women the presence of antibody reflects prior exposure to *C. trachomatis* and not ongoing infection. Symptoms from chlamydia are non-specific, without an abrupt onset or non-existent. Thus, most women will not have antibody tests performed at time when IgM antibody is present or a rise in IgG antibody can be demonstrated. Finally, cross-reaction takes place between *C. trachomatis* and *Chlamydia pneumonia* antibody that makes serologic diagnosis difficult.

Screening for chlamydia should be offered to women with suspected *C. trachomatis* genital infection based upon symptoms or signs of acute urethritis, cervicitis, endometritis, and salpingitis. Women with *Neisseria gonorrhoeae* also should be screened for *C. trachomatis* because these two infections often occur together. *C. trachomatis* should especially be sought in women with signs suggestive of cervical infection (mucopurulent endocervical discharge, endocervical bleeding and cervical ectopy). In addition, women exposed to men with gonorrhea or non-gonococcal urethritis should be screened for chlamydia. Confirmation of chlamydial infection improves the patient's understanding of the disease, probably enhances compliance and treatment of sexual partners.

Asymptomatic women at high risk for chlamydia should also be offered screening. Universal screening should occur of women attending STD, family planning and abortion clinics where the prevalence of infection is often over 10%. Selective screening may be a more effective strategy in clinical setting where the prevalence of chlamydia is <5%. Women candidates for selective screening in these clinics because of a high risk for chlamydia include those 21 years of age and younger, with a new sexual partner or multiple sexual partners, with non-white ethnicity, with single marital status and users of oral contraceptives.

TREATMENT OF CHLAMYDIA

Treatment of chlamydia includes seven or more days of antibiotics. Penicillin, ampicillin, cephalosporins and spectinomycin used in single doses to treat gonorrhea do not treat chlamydia. Non-pregnant women should receive either azithromycin 1 gram in a single dose or doxycycline 100 twice a day for 7 days [4]. Alternative regimens include seven days of erythromycin base 500 mg four times daily, erythromycin ethylsuccinate 800 gm four times daily or ofloxacin 300 mg twice daily. Male sexual partners of women with chlamydia should also be treated.

PREVENTION OF CHLAMYDIAL INFECTION

Since most chlamydial infections are asymptomatic, effective chlamydial control must include periodic testing of individuals at risk for infection. Ideally, all sexually active women would receive annual screening. However, cost of screening limits this approach at present. Women attending selected clinics that are high risk for chlamydia deserve universal screening. In cost-effective analyses, universal screening is preferred in settings with a chlamydial prevalence above about 5% (range 3 to 7%) [5]. Such clinics include STD, family planning, juvenile detention and abortion clinics. In other clinical settings with lower rates of chlamydia, infections are increased in women with age < 21; new, symptomatic or multiple sexual partners; evidence of cervical infection and, in some settings, non-white ethnicity. In some reports, screening based solely on age < 21 years was as sensitive as other criteria [6].

Selective screening has reduced the prevalence of chlamydia in several regions. In Region X (Northwest) of the U.S., extensive screening began in family planning clinics in 1988 and in STD clinics in 1992. The prevalence of *C. trachomatis* declined from 10 to 12% in the late 1980s to 4 to 5% by 1995 [1]. A decrease of 50% or more in the prevalence of *C. trachomatis* has also been documented following screening programs in Wisconsin [7] and Sweden [8]. Thus, screening programs are feasible and effective.

CHLAYMIDA AND SALPINGITIS

C. trachomatis is now established as an important etiological agent in acute and chronic salpingitis. *C. trachomatis* was isolated from the cervix of 29% of 1528 women (range was generally 25 to 50%) with pelvic inflammatory disease (PID) in 19 studies published between 1977 and 1992 [9]. As a comparison, *N. gonorrhoeae* was isolated from 26% of 1891 women with PID from 20 of these studies [9]. Patients with high rates of chlamydia tended to have lower rates of gonorrhea and vice versa. About 20 to 30% of patients with PID and *C. trachomatis* also have *N. gonorrhoeae*. Very little data are available using more sensitive LCR or PCR amplification methods to diagnose chlamydia among women with PID, but many investigators suspect that the actual prevalence of chlamydia in studies that used culture identification was 15 to 25% lower than reported prevalence rates.

INFERTILITY FOLLOWING SALPINGITIS

A wide proportion of infertility has been attributed to tubal obstruction from a prior episode of salpingitis. In studies from industrialized countries, 10 to 15% of women in infertile couples have documented tubal abnormalities and/ or pelvic adhesions [9]. By contrast about 2/3 of infertile African couples have these tubal abnormalities [10]. The most complete studies on infertility following salpingitis are from Lars Westrom's studies in Sweden [11]. In brief review of these studies, 1730 women underwent routine diagnostic laparoscopy for a clinically diagnoses acute salpingitis between 1960 and 1984. Salpingitis was present by laparoscopic criteria in 1282 women. Normal fallopian tubes and no other pelvic pathology at laparoscopy was present in 448 women who were used as controls. Women with salpingitis who exposed themselves to pregnancy during follow-up and either conceived or sought infertility treatment were compared to the 448 women with normal laparoscopic findings. An intrauterine pregnancy occurred in 97% of controls and 78% of patients with salpingitis after the index laparoscopy. Tubal factor infertility (TFI) occurred among 12% of the patients following salpingitis and in 1% of controls after the laparoscopy. Infertility from other reasons was present in 2% of the salpingitis and 1% of the control group. In these data, relative to controls, the relative risk (RR) of TFI increased 7-fold after one, 16-fold after two and 28 fold after three episodes of salpingitis [11]. Each episode of salpingitis caused about a doubling of the rate of TFI from a 12% rate of TFI following one episode. The RR of TFI was also related to the degree of tubal abnormality observed during the acute episode of salpingitis. Delay of over 3 days of abdominal pain increased TFI about 3-fold compared to those who presented for treatment earlier. However, antibiotic treatment used for the acute episode of salpingitis did not influence TFI [12]. It is not clear whether *C. trachomatis* is more likely than *N. gonorrhoeae* to cause TFI following salpingitis, but these data quantify the amount of TFI following well-documented salpingitis.

ECTOPIC PREGNANCY FOLLOWING SALPINGITIS

Ectopic pregnancy is also increased following salpingitis. Since only about half of women with one ectopic pregnancy have a subsequent pregnancy, ectopic pregnancy also has a dramatic impact upon infertility. In the Swedish data, the first pregnancy following laparoscopy was ectopic pregnancy in 1.3% of control women and 7.8% of those with salpingitis [11]. In a review, the prevalence of serum antibody to *C. trachomatis* was 60% (range 32-71) in patients with ectopic pregnancy and 24% (range 4-39) in controls [13].

REDUCTION OF SAPLINGITIS BY TREATMENT OF CHLAMYDIA

Evidence now exists that treatment of *C. trachomatis* prevents PID. Women in a large health maintenance organization who met selective chlamydia screening criteria were randomized to an intervention arm where women were invited to be tested and treated for chlamydial cervical infection and a control arm where routine screening was not provided and patients received their usual care [14]. The prevalence of chlamydia was low (3.5%) in this population. A significant reduction occurred in the 1-year incidence of symptomatic PID compared to the control group (odds ratio, .44, 95% CI .2-.9) even despite a low prevalence of chlamydia in the population.[14] Culture was used to identify chlamydia in this study, but new LCR and PCR amplification methods should make screening easier and more sensitive. Thus, screening and treating *C. trachomatis* also has been shown to reduce the rate of PID.

Respectfully submitted to the Prevention of Infertility Committee by:
David A. Eschenbach, M.D.

REFERENCES

1. Centers for Disease Control: *Chlamydia trachomatis* genital infection – United States, 1995. MMWR 1997;46:193-98.
2. Stamm WE. *Chlamydia trachomatis* infections of the adult. Holmes KK, Sparling PF, Mårdh P-A et al. (eds). In Sexually Transmitted Diseases McGraw-Hill, New York 1999, 407-22.
3. Pasternack R et al. Detection of CT infections in women by Amplicor PCR: comparison of diagnostic performance with urine and cervical specimens. J Clin Microbiol 1996;34:995-8.
4. 1998 guidelines for treatment of sexually transmitted diseases. MMWR 1998;47:53-9.
5. Marrazzo JM et al. Performance and cost-effectiveness of selective screening for chlamydial infection in women: Implications for a national screening strategy. Sex Transm Dis 1997;24:131-41.
6. Marrazzo JM et al. Selective screening criteria for chlamydial infection in women: a comparison of CDC screening recommendations with age and risk-based criteria. Fam Plann Perspect 1997;29158-62.
7. Addiss DG et al. Decreased prevalence of *Chlamydia trachomatis* infection associated with a selective screening program in family planning clinics in Wisconsin. Sex Transm Dis 1993;20:28-35.
8. Herrmann B, et al. Genital *Chlamydia trachomatis* (CT) infections in Uppsala County, Sweden 1985-1993: Has a changed STD legislation contributed to declining rates (Abst 259)? Eleventh Meeting of the International Society for STD Research. New Orleans, LS, August 1995.
9. Hull MG, et al. Population study of causes, treatment, and outcome of infertility. Br Med J 1985;291:1693.
10. Cates W, et al. Worldwide patterns of infertility. Is Africa different? Lancet 1985;2:596.
11. Westrom L, Eschenbach DA. Pelvic inflammatory disease. Holmes KK, Sparling PR, Mardh P-A et al. (eds). In Sexually Transmitted Diseases McGraw-Hill, New York 1999, 783-809.
12. Westrom L, et al. Infertility after acute salpingitis: Results of treatment with different antibiotics. Curr Ther Res 1979;26:752.
13. Westrom L. Consequences of Pelvic Inflammatory Disease, in Pelvic Inflammatory Disease, Berger GS, Westrom L (eds). New York, Raven Press, 1992,101.
14. Scholes D, Steragachis A, Heidrich FE, Andrilla H, Holmes KK, Stamm WE. Prevention of pelvic inflammatory disease by screening for cervical chlamydial infection. NEJM 1996;334:1362-6.