

## REVIEW ARTICLE

Edward W. Campion, M.D., *Editor*

## Pelvic Inflammatory Disease

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PELVIC INFLAMMATORY DISEASE IS AN INFECTION-INDUCED INFLAMMATION of the female upper reproductive tract (the endometrium, fallopian tubes, ovaries, or pelvic peritoneum); it has a wide range of clinical manifestations.<sup>1</sup> Inflammation spreads from the vagina or cervix to the upper genital tract, with endometritis as an intermediate stage in the pathogenesis of disease.<sup>2</sup> The hallmark of the diagnosis is pelvic tenderness combined with inflammation of the lower genital tract; women with pelvic inflammatory disease often have very subtle symptoms and signs.<sup>3</sup> Many women have clinically silent spread of infection to the upper genital tract, which results in subclinical pelvic inflammatory disease.<sup>1,4</sup>

Pelvic inflammatory disease is a major concern because it can result in long-term reproductive disability, including infertility, ectopic pregnancy, and chronic pelvic pain. After the introduction of laparoscopy in the 1960s, research on pelvic inflammatory disease proliferated through the 1970s, 1980s, and 1990s, leading to major breakthroughs in the understanding of the microbial causes of the disease and its relationship to reproductive disability, as well as enabling the standardization of antimicrobial treatment. According to a national estimate, in 2001 more than 750,000 cases of pelvic inflammatory disease occurred in the United States.<sup>5</sup> Over the past two decades, the rates and severity of pelvic inflammatory disease have declined in North America and western Europe.<sup>6-9</sup> These declines have occurred in association with public health efforts to control *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infection.<sup>6,10,11</sup> Despite progress, however, pelvic inflammatory disease remains a problem because reproductive outcomes among treated patients are still suboptimal, subclinical pelvic inflammatory disease remains poorly controlled, and programs aimed at the prevention of pelvic inflammatory disease are not feasible in much of the developing world.

## PATHOPHYSIOLOGY AND MICROBIAL CAUSES

Acute ( $\leq 30$  days' duration), clinically diagnosed pelvic inflammatory disease is caused by spontaneous ascension of microbes from the cervix or vagina to the endometrium, fallopian tubes, and adjacent structures. More than 85% of infections are due to sexually transmitted cervical pathogens or bacterial vaginosis-associated microbes, and approximately 15% are due to respiratory or enteric organisms that have colonized the lower genital tract (Table 1). Subclinical pelvic inflammatory disease has causes similar to those of acute pelvic inflammatory disease and may be twice as common.<sup>1,12</sup> Chronic ( $>30$  days' duration) pelvic inflammatory disease is defined as chronic infection due to *Mycobacterium tuberculosis* or actinomyces species rather than as chronic recurrent pelvic pain, which remains common after the treatment of acute pelvic inflammatory disease. This review focuses on acute and subclinical pelvic inflammatory disease.

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**Table 1. Clinical Classification of Pelvic Inflammatory Disease and Likely Microbial Causes.**

Clinical Syndrome	Causes
Acute pelvic inflammatory disease (≤30 days' duration)	Cervical pathogens ( <i>Neisseria gonorrhoeae</i> , <i>Chlamydia trachomatis</i> , and <i>Mycoplasma genitalium</i> ) Bacterial vaginosis pathogens (peptostreptococcus species, bacteroides species, atopobium species, leptotrichia species, <i>M. hominis</i> , <i>Ureaplasma urealyticum</i> , and clostridia species) Respiratory pathogens ( <i>Haemophilus influenzae</i> , <i>Streptococcus pneumoniae</i> , group A streptococci, and <i>Staphylococcus aureus</i> ) Enteric pathogens ( <i>Escherichia coli</i> , <i>Bacteroides fragilis</i> , group B streptococci, and campylobacter species)
Subclinical pelvic inflammatory disease	<i>C. trachomatis</i> and <i>N. gonorrhoeae</i>
Chronic pelvic inflammatory disease (>30 days' duration)	<i>Mycobacterium tuberculosis</i> and actinomyces species

Ascending infection from the cervix is often due to sexually acquired infections with *N. gonorrhoeae* or *C. trachomatis*. Sexually transmitted *Mycoplasma genitalium* has been identified as a likely cause of cervicitis, endometritis, salpingitis, and infertility, but the evidence has been inconsistent.<sup>13-15</sup> The factors determining which cervical infections ascend to the upper genital tract have not been completely elucidated, but data from prospective studies suggest that about 15% of untreated chlamydial infections progress to clinically diagnosed pelvic inflammatory disease.<sup>16-18</sup> The risk of pelvic inflammatory disease after gonococcal infection may be even higher. Sexual intercourse and retrograde menstruation may be particularly important in the movement of organisms from the lower to the upper genital tract.<sup>1</sup>

Anaerobic and facultative bacteria that are found in vaginal flora have been isolated alone or with *N. gonorrhoeae* and *C. trachomatis* infection in the fallopian tubes of women with acute pelvic inflammatory disease (Table 1).<sup>1,19-23</sup> These organisms occur in greater concentrations in association with bacterial vaginosis, a polymicrobial dysbiosis characterized by a reduction in normal vaginal lactobacilli and overgrowth of a much more complex anaerobic biofilm-associated microbiome.<sup>24</sup> Bacterial vaginosis is associated with local production of enzymes that degrade cervical mucus and associated antimicrobial peptides.<sup>3,25,26</sup> This degradation may impair the cervical barrier to ascending infection and facilitate the spread of microorganisms to the upper genital tract.<sup>27</sup>

Infection results in fibrinous or suppurative inflammatory damage along the epithelial surface of the fallopian tubes and the peritoneal surface

of the fallopian tubes and ovaries, which leads to scarring, adhesions, and possibly partial or total obstruction of the fallopian tubes. The adaptive immune response plays a role in the pathogenesis of pelvic inflammatory disease because reinfection substantially increases the risk of tubal-factor infertility (i.e., the inability to conceive because of structural or functional damage to the fallopian tubes). Infection-induced selective loss of ciliated epithelial cells along the fallopian tube epithelium can cause impaired ovum transport, resulting in tubal-factor infertility or ectopic pregnancy (Fig. 1).<sup>28</sup> Peritoneal adhesions along the fallopian tubes may prevent pregnancy, and adhesions within the pelvis are related to pelvic pain.

#### CLINICAL MANIFESTATIONS AND DIAGNOSIS

Pelvic inflammatory disease is particularly common among sexually active young and adolescent women, who are most often treated in ambulatory clinics, physician offices, or emergency departments.<sup>9,29-31</sup> The abrupt onset of severe lower abdominal pain during or shortly after menses has been the classic symptom used to identify acute pelvic inflammatory disease, although it is now well recognized that both the onset and severity of symptoms can be more ill-defined and subtle. Atypical, milder clinical manifestations have become more common as rates of *N. gonorrhoeae* infection have fallen.<sup>32,33</sup> The symptoms associated with acute pelvic inflammatory disease include pelvic or lower abdominal pain of varying severity, abnormal vaginal discharge, intermenstrual or postcoital bleeding, dyspareunia, and

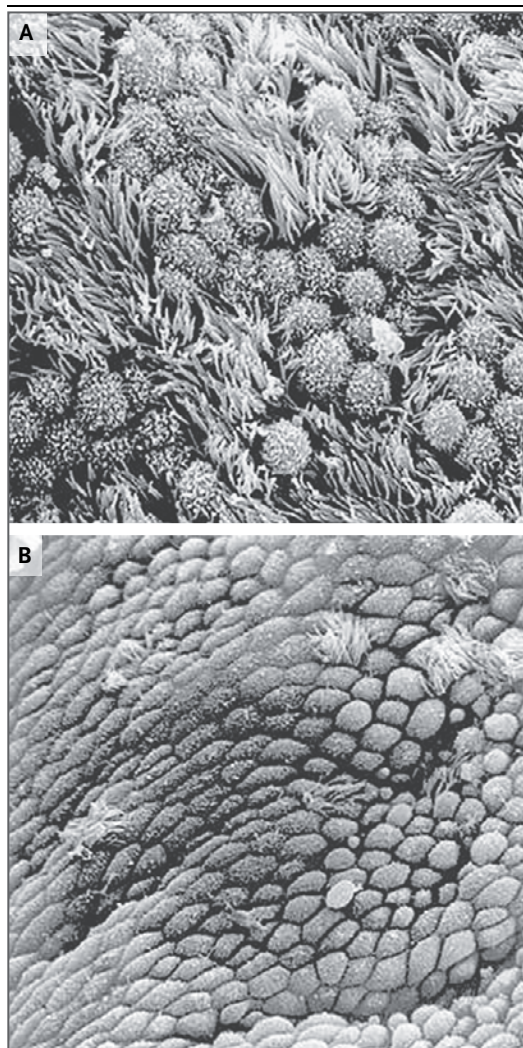
dysuria.<sup>34</sup> Fever can occur, but systemic manifestations are not a prominent feature of pelvic inflammatory disease. Occasionally, right-upper-quadrant pain suggestive of inflammation and adhesion formation in the liver capsule (perihepatitis or the Fitz-Hugh–Curtis syndrome) can accompany pelvic inflammatory disease.

A large body of evidence suggests that infection and inflammation in the upper genital tract can occur and lead to long-term reproductive complications in the absence of symptoms, a condition often called subclinical pelvic inflammatory disease.<sup>1,4,12</sup> Asymptomatic infections of the upper genital tract have been well documented,<sup>35</sup> and most women with tubal-factor infertility do not have a history of clinically diagnosed pelvic inflammatory disease, as has been observed in studies showing strong associations between infertility and serologic evidence of previous *C. trachomatis* or *N. gonorrhoeae* infection.<sup>36,37</sup> Among women with tubal-factor infertility, biopsy specimens show similar pathologic tubal damage in women who have a history of pelvic inflammatory disease and those who do not.<sup>28</sup> However, of note, in one study involving infertile women without a history of diagnosed pelvic inflammatory disease, 60% of the women with tubal-factor infertility, as compared with only 19% of those without tubal-factor infertility, reported health care visits for abdominal pain<sup>38</sup>; this suggests that many cases of pelvic inflammatory disease are missed and that clinicians should have a low threshold for considering the diagnosis.

The clinical diagnosis of pelvic inflammatory disease is based on the finding of pelvic organ tenderness, as indicated by cervical motion tenderness, adnexal tenderness, or uterine compression tenderness on bimanual examination, in conjunction with signs of lower genital tract inflammation. Signs of lower genital tract inflammation include cervical mucopus, which is visible as an exudate from the endocervix or as yellow or green mucus on a cotton-tipped swab placed gently into the cervical os (positive “swab test”); cervical friability (easily induced columnar epithelial bleeding); or increased numbers of white cells observed on saline microscopic examination of vaginal secretions (wet mount) (Fig. 2).<sup>39,40</sup> Pelvic tenderness of any kind has high sensitivity (>95%) for pelvic inflammatory disease, but it has poor specificity. Findings of lower genital tract inflammation increase the specificity of

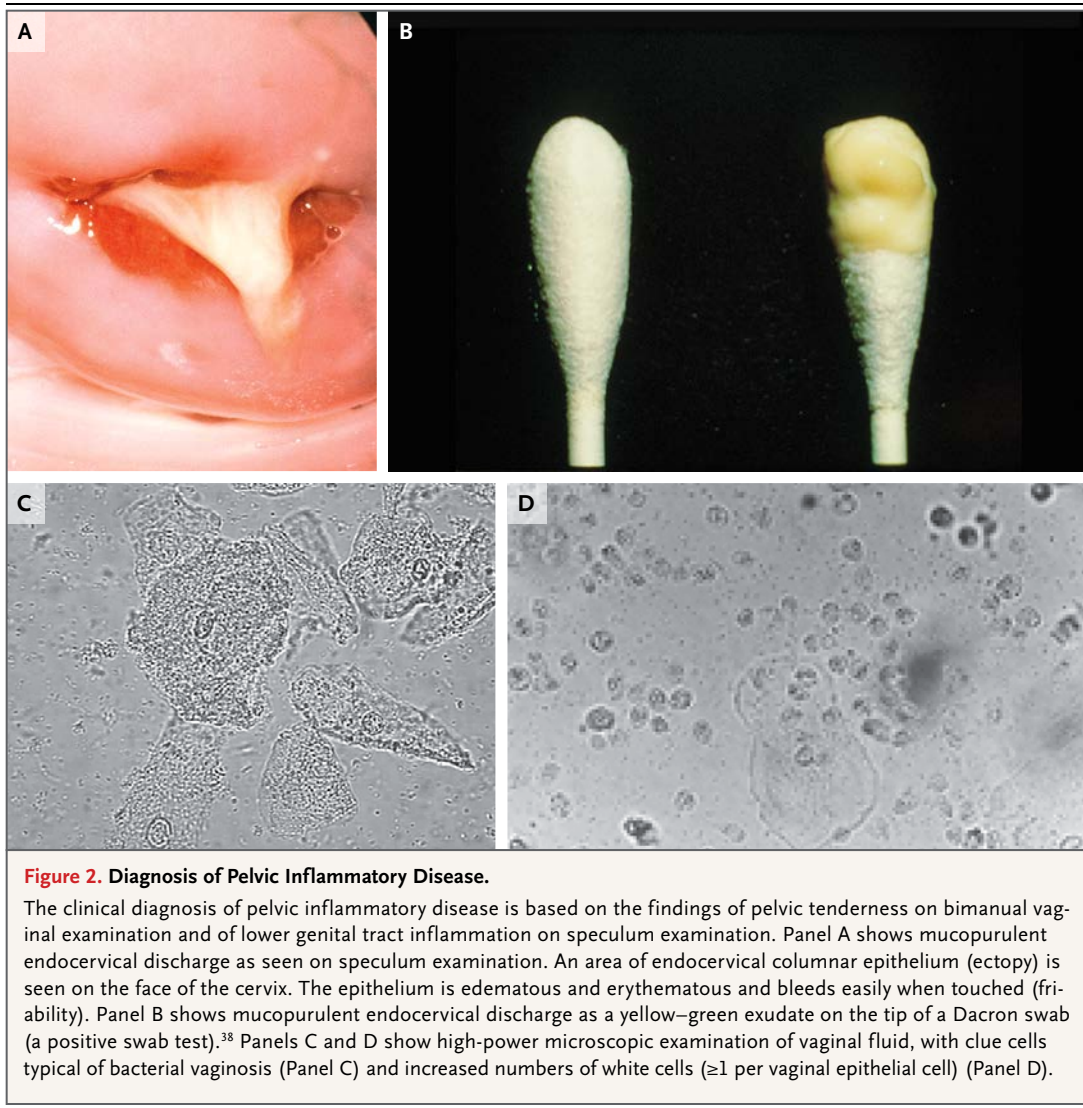
the diagnosis.<sup>41</sup> Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org, shows a simplified algorithm for guiding the clinical diagnosis of pelvic inflammatory disease.

Unfortunately, the clinical diagnosis of pelvic inflammatory disease is imprecise. Only about



**Figure 1. Pathologic Changes in the Epithelial Surface of the Fallopian Tube after Pelvic Inflammatory Disease.**

Scanning electron micrographs show normal human fallopian tube epithelia (Panel A) and the epithelial surface after pelvic inflammatory disease (Panel B). Pelvic inflammatory disease causes a selective loss of ciliated epithelial cells, which interferes with intratubal ovum transport, resulting in infertility or ectopic pregnancy. Images courtesy of Dorothy L. Patton, University of Washington, Seattle.



75% of women who have received a clinical diagnosis of pelvic inflammatory disease that is based on symptoms of pelvic tenderness and inflammation of the lower genital tract have laparoscopic confirmation of salpingitis (visualization of tubal and uterine inflammation, exudate, adhesions, or abscess).<sup>42</sup> Although laparoscopy has been considered the standard for the diagnosis of pelvic inflammatory disease, it has high interobserver variability<sup>43</sup> and might not detect endometritis or early tubal inflammation.<sup>44</sup> In addition, it is an invasive surgical procedure that is not readily available in many settings and is not routinely performed, especially in women with mild-to-moderate symptoms. Transcervical endometrial aspiration with histopathological

findings of increased numbers of plasma cells and neutrophils is more commonly used to confirm the diagnosis of pelvic inflammatory disease, and these findings are often seen in association with laparoscopically confirmed salpingitis.<sup>2</sup> However, endometrial biopsy is somewhat invasive, requires skill for the pathological interpretation of the sample, and results in a delayed diagnosis.<sup>45</sup> Transvaginal ultrasonography and magnetic resonance imaging (MRI) revealing thickened, fluid-filled tubes are available during the diagnostic workup and are highly specific for salpingitis.<sup>46,47</sup> However, the sensitivity of ultrasonography is only fair, and although MRI has high sensitivity, it is expensive and not typically available in resource-poor settings. Power Doppler studies show-

**Table 2. First-Line Antimicrobial Treatment Recommended by the Centers for Disease Control and Prevention (CDC) for Pelvic Inflammatory Disease.\***

**Outpatient regimen for mild-to-moderate pelvic inflammatory disease**

Doxycycline (100 mg orally twice daily for 2 wk) with or without metronidazole (500 mg orally twice daily for 2 wk), plus one of the following:

Ceftriaxone (250 mg intramuscularly in a single dose)

Cefoxitin (2 g intramuscularly) with probenecid (1 g orally) concurrently in a single dose

Other parenteral third-generation cephalosporin (cefotaxime or ceftizoxime)

**Inpatient regimen for moderate-to-severe pelvic inflammatory disease with or without tubo-ovarian abscess†**

One of the following:

Cefotetan (2 g intravenously every 12 hr) plus doxycycline (100 mg orally or intravenously every 12 hr)

Cefoxitin (2 g intravenously every 6 hr) plus doxycycline (100 mg orally or intravenously every 12 hr)

Clindamycin (900 mg intravenously every 8 hr) plus gentamicin (3 to 5 mg per kilogram of body weight intravenously once daily)

\* Complete treatment information, including alternative regimens and additional considerations, is available at the CDC website.<sup>33</sup>

† Transition to oral therapy can usually be initiated within 24 to 48 hours after clinical improvement, and oral therapy should be continued to complete 2 weeks of therapy.

ing increased fallopian-tube blood flow are highly suggestive of infection.<sup>46,48</sup> Imaging studies may also be useful in making an alternative diagnosis, such as ovarian cyst, endometriosis, ectopic pregnancy, or acute appendicitis; these conditions can be found in 10 to 25% of women who are thought to have acute pelvic inflammatory disease.

All patients with suspected pelvic inflammatory disease should undergo cervical or vaginal nucleic acid amplification tests for *N. gonorrhoeae* and *C. trachomatis* infection; if the results are positive, the probability that pelvic inflammatory disease is present increases substantially.<sup>41</sup> Molecular tests for *M. genitalium* are not yet commercially available. Vaginal fluid should be evaluated for increased numbers of white cells (more than one neutrophil per epithelial cell) and signs of bacterial vaginosis, including vaginal epithelial cells that have their cell margins obscured by attached bacteria (i.e., clue cells), an elevated pH, and an amine odor on addition of potassium hydroxide (positive “whiff” test).<sup>40</sup> Normally, bacterial vaginosis is a noninflammatory condition, and if white cells accompany clue cells, this suggests pelvic inflammatory disease. A pregnancy test should be routinely requested to help rule out ectopic pregnancy. Serologic testing for human immunodeficiency virus (HIV) should be performed; HIV increases the risk of a tubo-ovarian abscess.<sup>49</sup> An elevated erythrocyte sedi-

mentation rate or C-reactive protein level can increase the specificity of a pelvic inflammatory disease diagnosis.<sup>41</sup>

TREATMENT

Guidelines for the treatment of pelvic inflammatory disease have been developed by the Centers for Disease Control and Prevention (CDC) on the basis of the results of clinical trials and the consensus recommendations of expert clinicians (Table 2).<sup>33</sup> The treatment of pelvic inflammatory disease is empirical and involves the use of broad-spectrum combination regimens of antimicrobial agents to cover likely pathogens. Treatment should cover the principal pathogens, *N. gonorrhoeae* and *C. trachomatis*, regardless of the results of testing. The need to cover anaerobes has not been definitively established in randomized clinical trials, but because bacterial vaginosis is commonly found in women with pelvic inflammatory disease and anaerobes are often recovered from upper genital tract samples, antimicrobials with anaerobic coverage are recommended. Reliable coverage of *M. genitalium* is problematic, because the majority of strains are resistant to doxycycline. Moxifloxacin reliably eradicates *M. genitalium*<sup>13</sup>; however, *N. gonorrhoeae* has acquired quinolone resistance, and quinolone monotherapy for pelvic inflammatory disease is no longer routinely recommended.<sup>50</sup> Substitution of azithromycin for doxycycline

covers *M. genitalium* and simplifies dosing. However, in a recent trial of treatment for nongonococcal urethritis,<sup>51</sup> azithromycin was found to be less reliable than doxycycline for the eradication of *C. trachomatis*, so it remains an alternative regimen.

The Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) study showed that among women with mild-to-moderate pelvic inflammatory disease, the efficacy of cefoxitin–doxycycline therapy, with respect to both short-term and long-term complications, was similar in inpatient and outpatient settings.<sup>52</sup> The same held true for adolescents. The reasons for hospitalization for pelvic inflammatory disease currently include pregnancy, an inability to rule out competing diagnoses, severe illness combined with an inability to take oral medications, or tubal abscess.

Most patients are successfully treated as outpatients with single-dose intramuscular ceftriaxone, cefoxitin plus probenidicid, or another third-generation cephalosporin (cefotaxime or ceftizoxime), followed by oral doxycycline with or without metronidazole for 2 weeks (Table 2). For hospitalized patients, therapy with cefotetan or cefoxitin (administered parenterally until 24 to 48 hours after clinical improvement) together with doxycycline and followed by doxycycline with or without metronidazole to complete 2 weeks of treatment is recommended. A regimen of clindamycin and an aminoglycoside may be particularly appropriate for patients with a tubo-ovarian abscess. Adjunctive nonsteroidal anti-inflammatory drugs do not improve the clinical outcome.<sup>53</sup> Removal of an intrauterine device (IUD) does not hasten clinical resolution (and may delay it), and in most cases the IUD is left in place.<sup>54</sup>

#### LONG-TERM REPRODUCTIVE OUTCOMES

Although more than 90% of patients with pelvic inflammatory disease will have a clinical response to CDC-recommended treatment, the long-term outcome of treatment is still suboptimal. In classic studies conducted between 1960 and 1984, Westrom and colleagues followed 2501 Swedish women for several years after the women underwent laparoscopy and treatment for clinically suspected pelvic inflammatory disease; 1844 of the women (74%) had confirmed salpingitis.<sup>42</sup>

Infertility (i.e., an inability to conceive after 1 year of attempting to become pregnant) developed, overall, in 16% of the women with laparoscopically confirmed salpingitis, as compared with 2.7% of the women with clinically suspected pelvic inflammatory disease but no salpingitis. In addition, 9% of women with salpingitis had a subsequent ectopic pregnancy. The PEACH study provides more modern-day estimates of the risk of reproductive sequelae among 831 urban American women treated with cefoxitin and doxycycline for mild-to-moderate, clinically diagnosed pelvic inflammatory disease between 1996 and 1999.<sup>52</sup> After 3 years of follow-up, approximately 18% of the women reported infertility, 0.6% had an ectopic pregnancy, and 29% had chronic pelvic pain (pain reported at two or more consecutive visits 3 to 4 months apart during a period of 2 to 5 years); 15% of the women had recurrent pelvic inflammatory disease.<sup>55</sup> Both of these studies indicate that repeated episodes of pelvic inflammatory disease markedly worsen the reproductive outcomes. Of note, delayed care for pelvic inflammatory disease has also been strongly associated with worse long-term outcomes.<sup>56</sup> It remains unclear why the long-term outcome of treated pelvic inflammatory disease remains so dismal, given the high rates of clinical response. Perhaps infection-induced damage to the fallopian tubes has occurred by the time treatment is first given. This observation, together with the frequent occurrence of subclinical pelvic inflammatory disease, have highlighted the importance of recognizing prevention of pelvic inflammatory disease as a major public health priority.

#### PREVENTION

The most important public health measure for the prevention of pelvic inflammatory disease is the prevention and control of sexually transmitted infections with *C. trachomatis* or *N. gonorrhoeae*. Many high-income countries have implemented programs to screen and treat women for asymptomatic *C. trachomatis* infection, on the basis of evidence from randomized controlled trials indicating that screening for and treating cervical *C. trachomatis* infection can reduce a woman's risk of pelvic inflammatory disease by approximately 30 to 50% over 1 year.<sup>17,57,58</sup> The U.S. Preventive Services Task Force, CDC, and other professional organizations recommend annual *C. trachomatis*

screening for all sexually active women younger than 25 years of age and older women at increased risk for infection (e.g., women with multiple or new sex partners).<sup>33,59</sup> These groups also recommend testing for *N. gonorrhoeae* among women at increased risk for infection (e.g., women with multiple sex partners or previous gonorrhea infection and women living in communities with a high prevalence of disease).

Comprehensive sex education, promotion of the use of condoms, and provision of condoms are cornerstones of the prevention of sexually transmitted infection globally and also have benefits for the prevention of pelvic inflammatory disease. Data from the PEACH study showed that persistent condom use during follow-up was associated with reduced risks of recurrent pelvic inflammatory disease, chronic pelvic pain, and infertility.<sup>60</sup> In women with pelvic inflammatory disease due to *N. gonorrhoeae* or *C. trachomatis*, reinfection and repeat pelvic inflammatory disease are common. Thus, prompt evaluation and empirical treatment of male sex partners of women with pelvic inflammatory disease or cervical infection are essential. If sex partners cannot be linked to care, expedited treatment of the partner (e.g., providing prescriptions or medications to a patient to take to her partner, without the clinician examining the partner) is a useful approach and has been shown to reduce the risk of reinfection.<sup>61</sup>

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#### UNANSWERED QUESTIONS AND UNADDRESSED NEEDS

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The National Institutes of Health recently convened a workshop to identify research needs for the improvement of the diagnosis, treatment, and prevention of pelvic inflammatory disease (Table 3).<sup>62</sup> One of the most important needs for research regarding pelvic inflammatory disease and clinical care of women with the disease is the development of an accurate noninvasive or minimally invasive test to confirm infection of the fallopian tubes or inflammatory changes that predict long-term reproductive tract disease. Biomarkers of the immune response to *C. trachomatis* can predict tubal-factor infertility due to subclinical pelvic inflammatory disease.<sup>36,37</sup> However, additional biomarkers are needed. Levels of CA-125 and E-cadherin in serum correlate with the diagnosis of acute pelvic inflammatory dis-

ease and can be used to track the response to therapy.<sup>63,64</sup> Further study is needed before these assays are adopted into clinical practice. Immunohistochemical analysis and flow cytometry are being used to define specific cellular infiltrate patterns from endometrial biopsy specimens that correlate with infection.<sup>65</sup> Several studies that have assessed diagnostic imaging have shown the potential of MRI, transvaginal ultrasonography, and power Doppler imaging to improve the diagnosis of pelvic inflammatory disease,<sup>47</sup> but larger follow-up studies are needed to better define the role of these techniques in the treatment of symptomatic women and asymptomatic women with lower genital tract infection.

In recent studies in high-income populations, less than half the women with pelvic inflammatory disease have had evidence of *C. trachomatis* or *N. gonorrhoeae* infection, and the exact microbiologic cause of inflammation remains unclear.<sup>66</sup> *M. genitalium* and bacterial vaginosis-associated microbes have been implicated as potential causes. Confirmatory studies are necessary to define the independent role of *M. genitalium* in causing pelvic inflammatory disease and long-term sequelae.<sup>13</sup> The results of an ongoing clinical trial (ClinicalTrials.gov number, NCT01160640) evaluating the addition of metronidazole therapy to pelvic inflammatory disease regimens are expected in 2015 and should help clarify the role that organisms that cause bacterial vaginosis play in the pathogenesis of pelvic inflammatory disease. Anaerobic culture and deep sequencing methods are being used to identify specific bacterial vaginosis-associated organisms that may be more likely to cause pelvic inflammatory disease.

For financial and logistic reasons, pelvic inflammatory disease prevention programs that are based on screening are simply unavailable in most low-income and middle-income countries, where the burden of pelvic inflammatory disease may be greatest. The global epidemiologic profile of pelvic inflammatory disease has not been well defined. However, because an estimated 95.5 million *C. trachomatis* and *N. gonorrhoeae* infections occur globally among women each year<sup>67</sup> and approximately 15% of untreated infections lead to pelvic inflammatory disease,<sup>18</sup> the global burden of pelvic inflammatory disease is probably substantial. The proportion of infertility that is tubal-factor infertility — and thus caused primarily by scarring from genital infec-

**Table 3. Research Needs Identified by Clinicians, Public Health Professionals, and Researchers at a 2011 National Institutes of Health Workshop.\*****Characterize pathophysiological aspects of disease**

Determine whether *M. genitalium* and bacterial vaginosis–associated organisms play a causal role in pelvic inflammatory disease and its sequelae  
 Determine whether histopathological endometritis correlates with subclinical pelvic inflammatory disease and its sequelae

**Identify biomarkers**

Identify immune and other biomarkers that correlate with pelvic inflammatory disease and its sequelae, as well as non-invasive tests to detect and measure them

**Improve disease detection**

Develop polymicrobial tests for lower genital tract infection  
 Evaluate patient-administered diagnostic tests to improve case finding  
 Determine the individual and combined predictive values of *C. trachomatis* and *N. gonorrhoeae* detection, endometrial biopsy, and imaging (MRI and ultrasonography) for the detection of pelvic inflammatory disease

**Determine most effective treatment**

Determine benefits of antimicrobial coverage for anaerobes and mycoplasma species  
 Improve oral outpatient regimens  
 Determine benefits of immune-modulating agents

**Prevent reinfection**

Improve mechanisms of partner treatment

\* The table is adapted from Darville.<sup>62</sup>

tion — varies widely by setting. In the United States, tubal-factor infertility affects 14% of couples seeking assisted reproductive technology for infertility<sup>68</sup>; in sub-Saharan Africa, tubal-factor infertility may be present in 65 to 85% of women who seek infertility care.<sup>69,70</sup>

Most clinicians in low-income and middle-income settings rely on syndromic management (i.e., the use of genital-symptom algorithms to guide treatment) without diagnostic tests. Because most *C. trachomatis* and *N. gonorrhoeae* infections in women are asymptomatic, the majority of infections are missed. In addition, syndromic diagnosis of vaginal discharge is a poor predictor of *N. gonorrhoeae* and *C. trachomatis* cervical infection. Inexpensive, point-of-care diagnostic tests for *C. trachomatis* and *N. gonorrhoeae* that are easy to use in low-resource settings are urgently needed.<sup>71</sup> However, the costs and complexities of screening programs may still be prohibitive. In

addition, the specter of cephalosporin-resistant *N. gonorrhoeae* looms on the horizon. Thus, the World Health Organization has concluded that the development of vaccines against *C. trachomatis* and *N. gonorrhoeae* is a critical priority for the prevention of pelvic inflammatory disease and its long-term sequelae globally.<sup>72</sup> Progress is most advanced for *C. trachomatis*, for which subunit, live, and inactivated vaccines have emerged from basic research for further clinical development.<sup>73</sup> Vaccines and other strategies to prevent pelvic inflammatory disease lie at the heart of efforts to improve women's reproductive health globally.

Dr. Brunham reports holding pending patents (WO/2013/044398; US 0027793, and PCT WO/2010/085896, CAN, US, EU, AU) related to chlamydia-specific proteins that may compose a *Chlamydia trachomatis* vaccine. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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