Pelvic Inflammatory Disease

Current Concepts in Pathogenesis, Diagnosis and Treatment

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KEYWORDS

- Pelvic inflammatory disease • *Neisseria gonorrhoeae* • *Chlamydia trachomatis*
- Cervical infection

KEY POINTS

- The diagnosis of pelvic inflammatory disease (PID) is based on clinical findings and requires a high index of suspicion.
- PID is caused both by common sexually transmitted infections, such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, and by anaerobic vaginal microbes.
- Antibiotic coverage for anaerobic bacteria should be considered when treating severe PID.
- Early identification and treatment of cervical infections can prevent PID.

Pelvic inflammatory disease (PID) is characterized by infection and inflammation of the upper genital tract in women: the uterus, fallopian tubes, and/or ovaries. Although a definitive diagnosis of PID can be made by laparoscopic visualization of inflamed, purulent fallopian tubes, PID is generally a clinical diagnosis and thus represents a diagnostic challenge. Because PID can cause significant reproductive health sequelae for women, diagnosis and treatment algorithms advise a high index of suspicion for PID in any woman of reproductive age with pelvic or abdominal pain, and err on the side of recommending what likely amounts to overtreatment with antibiotic regimens.

EPIDEMIOLOGY

In the United States in 2000, there were an estimated 1.2 million medical visits for PID,[1] a number that has been decreasing since 1985.[2–4] This decrease is attributed in part to widespread adoption of screening for *Chlamydia trachomatis*, the goal of which is to identify and treat asymptomatic cases of cervicitis before they can progress to PID.[5]

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Estimated direct medical costs associated with PID and its sequelae (ectopic pregnancy, chronic pelvic pain, and tubal infertility) were as high as US$1.88 billion in 1998, even though most women receive care as outpatients.[6]

Risk factors for PID are the same as those for acquisition of sexually transmitted diseases: multiple sexual partners, young age, smoking, and illicit drug use.[6–9] Douching has been implicated in some studies, and has been observed to double a woman's risk of upper genital tract infection.[8,10,11] Oral contraceptive use has been associated with lower rates of clinical PID, although it is not clear whether this is due to fewer infections or fewer symptoms, and thus underdiagnosis.[12–14] Bacterial vaginosis (BV) has also been associated with PID, though primarily in cross-sectional studies unable to determine causality.[15] In the prospective Gyn Infections Follow-Through study (GIFT), women with BV at enrollment did not have higher risk for PID over 4 years of follow-up, although women with *Neisseria gonorrhoeae* and *C trachomatis* did.[16]

ETIOLOGY

In early studies of PID, *N gonorrhoeae* was the most commonly isolated pathogen, and is still more likely than other pathogens to cause severe symptoms.[13,17–19] However, as the prevalence of gonorrhea has decreased, its importance as a causal agent for PID has diminished.[20,21] *C trachomatis* remains a significant pathogen associated with PID, detected in up to 60% of women with confirmed salpingitis or endometritis.[22–24] *Mycoplasma genitalium* has been independently associated with PID, although its prevalence is low in most populations that have been studied (this is further discussed in the article by Manhart elsewhere in this issue).[25,26] The proportion of cases of PID that involve nongonococcal, nonchlamydial etiology ranges between 9% and 23% in women with confirmed salpingitis or endometritis, even as diagnostic testing for gonorrhea and chlamydia become more sensitive.[7,22,24,27,28] In these cases, the microbial community is often diverse and includes anaerobes such as *Peptostreptococcus* spp and *Prevotella* spp.[23,27] Even in women with gonorrhea or chlamydia, detection of anaerobes in the upper genital tract is frequent and is associated with more severe disease.[16,22] In a study of Kenyan women with laparoscopically confirmed salpingitis, polymerase chain reaction assay of tubal samples for the bacterial 16S rRNA gene identified multiple species, including several associated with BV such as *Atopobium vaginae*, *Leptotrichia* spp, *Peptostreptococcus* spp, and *Prevotella* spp.[29]

PATHOGENESIS

Mathematical modeling based on epidemiologic and microbiologic studies suggests that 8% to 10% of women with *C trachomatis* infection will develop PID if not treated,[30] although in studies that followed women with chlamydial endocervical infection without treatment, the rate was even lower.[31,32] When both the lower and upper genital tract are sampled there is a clear gradient of infections, with a higher proportion of women testing positive at the vagina and/or cervix, fewer in the endometrium, and less frequently in the fallopian tubes.[23,24,27] One component of protection from bacterial ascent is the physical barrier of the cervix and its mucus barrier. Endometrial detection of gonorrhea or chlamydia is more frequent in the proliferative phase of the menstrual cycle[18] when cervical mucus is thinner[33] and the peristaltic contractions of the uterus move fluid cephalad.[34] There is also likely an immunologic component to the cervical barrier; genetic polymorphisms in toll-like receptor (TLR) genes seem to increase the risk of upper genital tract infection,[24] as do certain human leukocyte antigen class II alleles, suggesting that individual differences in immune function may increase the risk of developing PID in the setting of cervical infection.

Tubal damage is best described in the context of chlamydial infection, and appears to be related both to an innate immune inflammatory response initiated by the epithelial cells infected by *C trachomatis*[35] and to an adaptive T-cell response.[36,37] Although antibody titers to chlamydial antigens are increased in severe disease,[38,39] higher titers have not been associated with worse reproductive outcomes.[40] In human studies, evaluation of tubal inflammation is difficult without surgical intervention; thus, many studies use endometritis as a marker for tubal inflammation. Kiviat and colleagues[41] correlated the presence of both neutrophils and plasma cells in endometrial biopsies with visible salpingitis. In a cohort of women with mild to moderate PID who were treated with broad-spectrum antibiotics, the presence of either neutrophils or plasma cells in an endometrial biopsy was not associated with decreased fertility.[42] Plasma cells alone were found in 33% of endometrial samples of low-risk women[43] and were not associated with laparoscopic abnormalities; however, in women at high risk of sexually transmitted infections, plasma cell endometritis appears to be associated with decreased fertility.[44] The heterogeneity of these findings suggests that there is a range of individual immune response to upper genital tract infection, and that not all women have the same likelihood of reproductive sequelae from PID.

CLINICAL EVALUATION AND DIFFERENTIAL DIAGNOSIS

In practical terms, when a sexually active woman presents to the clinic or emergency department with lower abdominal or pelvic pain, PID must be considered in the differential diagnosis, which also includes appendicitis, ectopic pregnancy, ovarian torsion, intrapelvic bleeding, rupture of an adnexal mass, endometriosis, and gastroenteritis.[45] Key components of the physical examination include:

1. Abdominal examination, including palpation of the right upper quadrant
2. Vaginal speculum examination, including inspection of the cervix for friability and mucopurulent cervical discharge
3. Bimanual examination, assessing for cervical motion, uterine or adnexal tenderness, and pelvic masses
4. Microscopic evaluation of a sample of cervicovaginal discharge to assess for *Trichomonas vaginalis*, BV, and/or leukorrhea

The clinical presentation of PID is variable (**Table 1**), so a high index of suspicion is necessary. Symptoms may differ depending on the pathogens responsible. In the PID Evaluation and Clinical Health (PEACH) trial, women with PID associated with *C trachomatis* or *M genitalium* took almost 1 week longer to present to care than women with gonorrhea-associated PID, suggesting milder symptoms.[19] Women with gonococcal

Table 1
Prevalence of signs and symptoms in women with confirmed salpingitis or endometritis

Symptom	Prevalence (%)	Reference
Temperature >38.5°C	33–34	47,49
WBC >10,000 cells/mL	36–70	49,50
ESR >15 mm/h	36–77	49,50
Mucopurulent cervical discharge	56	49
Leukorrhea (≥10 WBC/hpf on wet mount)	22.1	53
Irregular vaginal bleeding	36–64	47,50

Abbreviations: ESR, erythrocyte sedimentation rate; hpf, high-power field; WBC, white blood cells.

infection are more likely to have fever, adnexal tenderness, mucopurulent cervicitis, and an elevated peripheral white blood cell (WBC) count.[46]

SENSITIVITY AND SPECIFICITY OF CDC DIAGNOSTIC CRITERIA

The clinical diagnosis of PID is based on recommendations from the Centers for Disease Control and Prevention (CDC). Minimum diagnostic criteria (**Box 1**) have been set with a high sensitivity and low specificity in order to detect as many cases of clinical disease as possible, thus potentially avoiding the long-term reproductive sequelae and economic costs associated with delayed diagnosis and lack of treatment.

In a cohort of patients with suspected PID who underwent laparoscopy in Lund, Sweden, PID was considered when a patient presented with lower abdominal pain and at least 2 of the following: abnormal vaginal discharge, fever, vomiting, menstrual irregularities, urinary symptoms, proctitis symptoms, marked tenderness of the pelvic organs on bimanual examination, palpable adnexal mass, or erythrocyte sedimentation rate (ESR) greater than 15 mm/h. Only 65% of women suspected to have PID using these criteria actually had salpingitis.[47] A 2003 reanalysis of data from this cohort demonstrated that the combination of fever (temperature >38.3°C), elevated ESR, and adnexal tenderness achieved the highest combination of sensitivity and specificity, 65% and 66%, respectively, for acute salpingitis.[48] In other words, these criteria would have a 35% false-negative rate for predicting laparoscopically determined PID.

It is difficult to calculate the exact sensitivity and specificity of the CDC diagnostic criteria, as there at least 2 potential gold standards for a true positive diagnosis of PID: salpingitis at laparoscopy or endometritis on endometrial biopsy. Because laparoscopy is expensive, invasive, and not part of a standard evaluation of PID, many

Box 1
CDC criteria for PID diagnosis

Minimum Criteria (At Least 1 Needed for Diagnosis)	Additional Criteria (Support a Diagnosis of PID)	Definitive Criteria (Confirm the Diagnosis of PID)
• Cervical motion tenderness • Uterine tenderness • Adnexal tenderness	• Oral temperature higher than 101°F/38.3°C • Abnormal vaginal or cervical discharge • White blood cells on saline wet mount (>10 polymorphonuclear leukocytes per high-power field[101]) • Elevated erythrocyte sedimentation rate (>15 mm/h) • Elevated C-reactive protein • Elevated white blood cell count higher than 10,000 cells/mL • Laboratory evidence of *Neisseria gonorrhoeae* or *Chlamydia trachomatis* infection	• Histopathologic evidence of endometritis • Imaging showing thickened, fluid-filled tubes, with or without pelvic free fluid or tubo-ovarian complex • Doppler studies suggesting pelvic infection • Intra-abdominal findings consistent with PID on laparoscopy

Adapted from Workowski KA, Berman S. Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59(RR-12):1–110.

studies use endometritis as a marker of upper genital tract infection and inflammation. Endometritis and salpingitis are correlated; histologic endometritis has sensitivity of 89% to 92% and specificity of 63% to 87% for laparoscopically diagnosed acute salpingitis, with only 7% to 22% of patients with clinically suspected PID having salpingitis without endometritis.[28,41,49,50] However, whereas the presence and severity of salpingitis is correlated with a risk of ectopic pregnancy and infertility,[21] endometritis is not as consistently associated with these outcomes[42]; this may be because not all women with endometritis have salpingitis (**Table 2**), thus diluting the association.

LABORATORY TESTING

Because PID is a clinical diagnosis, laboratory data or imaging studies are not usually necessary, but can be helpful in establishing the diagnosis or in defining its severity.[51] In the PEACH trial, which enrolled women with abdominal pain, pelvic tenderness, and evidence of lower genital tract inflammation, an elevated leukocyte count ($\geq$10,000 cells/mL) had 41% sensitivity and 76% specificity for the presence of endometritis.[52] The presence of 1 or more neutrophils per 1000$\times$ field saline wet mount of vaginal discharge had 91% sensitivity and 26.3% specificity for endometritis.[53] In another cohort study, an elevated ESR (>15 mm/h) had 70% sensitivity and 52% specificity for endometritis or salpingitis. Elevated WBC had 57% sensitivity and 88% specificity, whereas the presence of increased numbers of vaginal neutrophils ($\geq$3 per high-power field) had 78% sensitivity and 39% specificity.[54] In a cohort of women at high risk for pelvic infections, absence of vaginal WBCs had excellent negative predictive value (95%).[53] These data suggest that if an evaluation of a saline microscopy of vaginal fluid reveals no WBCs (leukorrhea), an alternative diagnosis to PID should be considered.

IMAGING STUDIES

Ultrasonography can also be used to aid in the diagnosis of PID and its direct treatment. A finding of thickened, fluid-filled tubes has 85% sensitivity and 100% specificity for endometritis among women with clinically diagnosed PID.[55] Timor-Tritsch and colleagues[56] detailed the various transvaginal sonographic markers of acute tubal inflammatory disease, including dilated tubal shape, abnormal wall structure, increased wall thickness ($\geq$5 mm), and presence of pelvic peritoneal fluid (free fluid or inclusion cyst). In a study comparing 30 patients with clinical PID confirmed with laparoscopy and 20 normal women, power Doppler demonstrating tubal hyperemia was 100% sensitive and 80% specific for PID; in addition, altered tubal shape, structure, and wall thickness were seen in an overwhelming majority of patients with pyosalpinx.[57] Magnetic resonance imaging, with its highly sensitive and specific ability to identify thickened,

Table 2
Incidence of endometritis and salpingitis among women with suspected PID and both laparoscopic and endometrial evaluation

Authors,[Ref.] Year	Endometritis Alone	Salpingitis Alone	Endometritis + Salpingitis
Paavonen et al,[102] 1985	3/27 (11.1%)	2/27 (7.4%)	16/27 (59.3%)
Wasserheit et al,[28] 1986	8/33 (24.2%)	1/33 (3.0%)	14/33 (42.4%)
Eckert et al,[49] 2002	26/152 (17.1%)	11/144 (7.6%)	64/144 (44.4%)

fluid-filled tubes, pyosalpinx, pelvic free fluid, and tubo-ovarian abscess (TOA), has also been proposed as a diagnostic modality for PID; however, it is very costly and not easily accessible or applicable to women seeking outpatient evaluation for possible PID.[58]

INPATIENT VERSUS OUTPATIENT MANAGEMENT

The therapeutic goal for the treatment of PID is 2-fold: short-term microbiologic and clinical cure; and long-term prevention of sequelae, namely tubal infertility, ectopic pregnancy, and chronic pelvic pain. Since the 1980s, PID therapy has shifted from the inpatient to the outpatient setting, with a 68% decline in hospitalization[4] attributable in part to several studies showing equivalent short-term outcomes with outpatient versus inpatient therapy for mild to moderate PID.[59,60] Between 1995 and 2001, 89% of all PID visits occurred in the ambulatory setting.[4] Current criteria for inpatient hospitalization are summarized in **Box 2**.

The PEACH trial compared inpatient administration of parenteral cefoxitin and doxycycline (parenteral/oral) with outpatient administration of intramuscular cefoxitin and oral doxycycline, and found no short-term (30-day) differences in microbiologic or clinical cure[61] or long-term differences in reproductive health outcomes (**Table 3**).[62] A secondary analysis among participants of the PEACH trial also found no long-term outcome differences by treatment group among those with clinically confirmed endometritis or upper genital tract gonorrheal or chlamydial infection.[61,62] Of interest, a representative subpopulation from PEACH revealed a 70% mean treatment adherence rate, with only 17% of participants taking doxycycline exactly as prescribed.[63] Similar rates of poor adherence to doxycycline or tetracycline prescribed for outpatient therapy for sexually transmitted infections (STIs) have been seen, particularly in the setting of gastrointestinal side effects.[64,65] This finding may explain the relatively high rates of ongoing disease and long-term sequelae in the PEACH cohort.

Whereas many of the original efficacy studies mandated inpatient intravenous treatment of 48 to 96 hours before switching to oral therapy,[61,66] current practice is to treat with intravenous medications until there is clinical improvement for 24 hours or more. However, because intravenous doxycycline can cause significant phlebitis and its oral bioavailability is comparable with that of parenteral bioavailability, an earlier switch to oral doxycycline can be made if a patient is tolerating oral medications.[61]

CDC RECOMMENDATIONS FOR ANTIMICROBIAL THERAPY

Current recommendations for antimicrobial treatment regimens in PID were published in 2010 (**Table 4**), and are scheduled for update in 2014.[67] A guiding principle for selection of antimicrobial therapy for PID is that the regimen should cover *N gonorrhoeae*

Box 2
Criteria for inpatient management of PID

- Surgical emergencies cannot be ruled out
- Pregnancy
- Lack of clinical response to oral antimicrobial PID therapy after 72 hours
- Inability to tolerate or comply with outpatient management
- Severe illness, high fever, nausea, vomiting
- Presence of tubo-ovarian abscess

Table 3
Summary of short-term and long-term effects of outpatient compared with inpatient therapy for mild to moderate PID in the PEACH trial

	Outpatient (%)	Inpatient (%)	*P* Value
Short Term (30 d)			
Gonorrhea positive	3.9	2.4	.44
Chlamydia positive	2.7	3.6	.52
Persistent tenderness	20.6	18.4	.50
Endometritis	45.9	37.6	.09
Long Term (mean 35 mo)			
Pregnancy	59.4	55.6	NS
Ectopic	1.2	0.2	NS
Infertility	16.7	20.6	NS
Chronic pelvic pain	40.7	44.6	NS
Recurrent PID	18.4	24.3	NS

Abbreviation: NS, not statistically significant.

Adapted from Ness RB, Soper DE, Holley RL, et al. Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease: results from the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) randomized trial. Am J Obstet Gynecol 2002;186(5):929–37; and Ness RB, Trautmann G, Richter HE, et al. Effectiveness of treatment strategies of some women with pelvic inflammatory disease: a randomized trial. Obstet Gynecol 2005;106(3):573–80.

and *C trachomatis*, regardless of results of diagnostic testing for these pathogens. Therapy for gonorrhea, and therefore PID, shifted away from fluoroquinolone-based regimens between the 2006 and 2010 iterations of the CDC Treatment Guidelines, given the rapid emergence of fluoroquinolone resistance.[68] In 2012, after reports of increasing prevalence of cefixime-resistant gonorrhea, the guidelines were changed again to drop cefixime as one of the first-line outpatient treatment options for cervicitis.[69] With additional cephalosporin resistance to gonorrhea reported, as discussed in the article by Barbee and Dombrowski elsewhere in this issue, the potential for development of resistance that could compromise treatment of gonorrhea-associated PID is of great concern.

ALTERNATIVE ANTIMICROBIAL REGIMENS

Although not part of the CDC recommendations, newer data suggest that parenteral followed by oral azithromycin, either as monotherapy or in combination with doxycycline and metronidazole, produces clinical cure rates of 97% to 98% at 2 weeks after initiation of treatment, and microbiologic cure rates of 90% to 94% at 6 weeks post-treatment.[70] The azithromycin-based regimens were compared with third-generation cephalosporin-based regimens or parenteral amoxicillin-based regimens and showed no statistically significant difference in clinical or microbiologic cure rates, although the study had a high dropout rate and low proportion of anaerobic bacteria isolated from endocervix and endometrium.[70] Another trial compared intramuscular ceftriaxone plus oral azithromycin with the standard of oral doxycycline, and found higher rates of clinical and histologic cure with azithromycin, although rates of cure in both arms were less than 80%.[71]

M genitalium is neither tested for nor considered when choosing therapy. However, newer evidence suggests a greater than 4-fold higher risk of treatment failure with

Table 4
Reported efficacy of CDC-recommended treatment regimens for inpatient and outpatient management of PID

	Response to Treatment (%)	Reference
Inpatient		
Cefotetan 2 g IV q 12 h AND Doxycycline 100 mg PO/IV q 12 h[a,b] Followed by doxycycline 100 mg PO BID for a total of 14 d	89–94	66,103
Cefoxitin 2 g IV q 6 h AND Doxycycline 100 mg PO/IV q 12 h[a,b] Followed by doxycycline 100 mg PO BID for a total of 14 d	84–95	61,103–106
Clindamycin 900 mg IV q 8 h AND Gentamicin 2 mg/kg IV/IM load then 1.5 mg/kg maintenance OR 3–5 mg/kg daily dosing Followed by doxycycline 100 mg PO BID OR Clindamycin 450 mg PO QID,[c] total 14-d course	84–90	66,104,106
Ampicillin/sulbactam 3 g IV q 6 h AND Doxycycline 100 mg PO/IV q 12 h[a,b] Followed by doxycycline 100 mg PO BID, total 14-d course	85–94[d]	71,105
Outpatient[e]		
Ceftriaxone 250 mg IM once AND Doxycycline 100 mg PO BID, total 14 d	72–95	60,70,107
Cefoxitin 2 mg IM once, with probenecid 1 g PO once AND Doxycycline 100 mg PO BID, total 14 d	90	61
Other parenteral third-generation cephalosporin (cefotaxime, ceftizoxime) AND Doxycycline 100 mg PO BID, total 14 d	—	—

Abbreviations: BID, twice daily; IM, intramuscular; IV, intravenous; PO, by mouth; q, every; QID, 4 times daily.

[a] Equivalent oral and IV bioavailability for doxycycline. IV doxycycline causes burning, therefore elect for oral doxycycline if able to be tolerated.

[b] Must add clindamycin 450 mg PO QID or metronidazole 500 mg PO q 6 h in the setting of tubo-ovarian abscess, for a total 14-day course.

[c] Continue clindamycin in the setting of tubo-ovarian abscess.

[d] Higher end of range is a regimen including metronidazole.

[e] For all 3 regimens, consider adding metronidazole 500 mg PO BID for 7 days.

a cefoxitin/doxycycline regimen when *M genitalium* is present, although there were no differences in reproductive sequelae or recurrent PID, as discussed in the article by Manhart elsewhere in this issue.[72] Doxycycline has poor efficacy against *M genitalium* (cure rates from 17% to 94%), and although azithromycin is more effective (67%–100% cure), moxifloxacin seems to be the most effective treatment.[73] In cases of persistent PID not responsive to standard therapy, testing for and treatment of *M genitalium* should be considered, and presumptive therapy with moxifloxacin may be warranted.

ANAEROBES: TO COVER OR NOT?

There is little clarity on the need for empiric coverage for anaerobic bacteria when PID is diagnosed, in part because there is a lack of clear understanding of the contribution of anaerobes to pathogenesis in PID. Several studies have shown that BV is associated with PID, with BV-associated anaerobic bacteria present in endometritis, but that BV

may not actually cause acute PID.[16,61,74] However, other data have not shown any long-term reproductive sequelae of histologically diagnosed anaerobic endometritis, even when treatment with a cephalosporin-based regimen with poor anaerobic coverage was provided.[42] Few studies have specifically examined microbiologic cure rates of antimicrobial treatment regimens targeting anaerobic bacteria. Some BV-associated microbes may form a biofilm on the endometrial surface, which could limit the ability of antibiotics to eliminate colonization.[75] The CDC currently recommends consideration of treatment regimens with anaerobic coverage until data suggest equivalent prevention of reproductive sequelae in treatment regimens lacking anaerobic coverage.[67] Anaerobic coverage should be included in women with a TOA and with BV, regardless of the latter's potential etiologic role in the development of acute PID.[67,76]

ADDITIONAL TREATMENT CONSIDERATIONS

Among patients who qualified for outpatient therapy, reevaluation of clinical status should occur within 72 hours, or sooner if indicated. If no meaningful clinical response is detected, patients with PID may require inpatient hospitalization, transition to parenteral antibiotics, further diagnostic tests including additional laboratory studies and imaging to evaluate for possible TOA, and possible surgical intervention.

Empiric treatment of gonorrhea and chlamydia is recommended for all male sexual partners within the past 60 days, or the most recent sexual partner if more than 60 days ago, regardless of symptoms or the result of gonorrhea and chlamydia testing in the female patient with PID.[67] Women diagnosed with PID should be offered a test for human immunodeficiency virus (HIV) at the time of diagnosis. Repeat testing for gonorrhea or chlamydia in 3 to 6 months is recommended if initial testing is positive for either infection.[67]

TUBO-OVARIAN ABSCESS

Although the presenting signs and symptoms of a TOA are not often distinct from those with salpingitis/endometritis, there are often more objective signs of infection and inflammation. A large series of patients with ultrasonographically or surgically confirmed TOA found that 60% had a temperature higher than 37.8°C, 68% had leukocytosis (>10,000 cells/mL), 26% had nausea, and 19% had chronic abdominopelvic pain.[77] In women with PID, palpation of an adnexal mass on physical examination, significant pain limiting proper evaluation of the adnexa, severe illness, or lack of clinical response to antimicrobial therapy should prompt imaging studies. In addition, imaging can help to evaluate for alternative diagnoses such as appendicitis, ovarian torsion, or cyst rupture.

Inpatient observation is recommended for at least 24 hours among hemodynamically stable women with a TOA, with the aim of observing for early signs of sepsis or potential abscess rupture. Surgical exploration on initial evaluation is indicated in the setting of an acute abdomen and signs of sepsis or hemodynamic instability, particularly if a ruptured TOA is suspected. Antimicrobial therapy should be parenteral to begin with, and should include clindamycin or metronidazole to cover anaerobes.[67] Antimicrobial therapy alone, with appropriate anaerobic coverage and the ability to penetrate and function in abscess cavities, is effective in 70% to 84% of women.[77,78]

In one cohort of women admitted with TOA, 60% of those with an abscess larger than 10 cm needed surgical management, compared with 20% of those with abscesses of 4 to 6 cm.[78] When no clinical improvement is noted within 72 hours of antibiotic initiation, minimally invasive drainage of the abscess or surgical management can be pursued; however, significant clinical deterioration at any time usually indicates the need for surgical exploration.[77] A study of empiric transvaginal ultrasound-guided aspiration of

TOAs at the time of diagnosis, in concert with antimicrobial therapy, revealed that the procedure is safe and well tolerated, and averted surgical management in 93% of cases.[79,80]

SPECIAL POPULATIONS: HIV-INFECTED WOMEN

The presenting signs and symptoms of PID generally do not differ significantly by HIV infection status,[81,82] although some studies have demonstrated an increased odds of fever, higher clinical severity scores, and higher likelihood of having a TOA among HIV-infected women.[83–85] Clinical severity has been found to correlate with immunosuppression among HIV-infected women with laparoscopically confirmed PID.[83]

Treatment of PID or TOA has been shown to be as effective in HIV-infected women as in uninfected women.[81,83,84,86] In a prospective study, the 12% clinical failure rate of outpatient therapy was not predicted by HIV serostatus.[81] Duration of hospitalization and antibiotic therapy also did not differ by HIV serostatus; however, among HIV-infected women, immunosuppressed patients required longer inpatient therapy and antibiotic regimens.[83]

SPECIAL POPULATIONS: POSTMENOPAUSAL WOMEN

Although rare, postmenopausal women can develop PID, presenting most commonly with lower abdominal pain and postmenopausal bleeding, as well as fever, nausea, and altered bowel habits; they are considerably more likely to have TOAs.[87,88] Among 20 postmenopausal women with TOAs in one case series, although only 20% of patients were febrile, 45% had elevated WBC counts, 55% had a palpable pelvic mass, and 90% had a TOA on surgical exploration.[89] In several small case series, pathologic analysis of the surgical specimens revealed a concurrent gynecologic malignancy (cervix, endometrium, or ovary) in 40% to 47% of the patients.[88–90] Based on these data, any postmenopausal woman with PID should be evaluated for the presence of a pelvic cancer.

SPECIAL POPULATIONS: INTRAUTERINE DEVICES

In the 1970s the Dalkon Shield intrauterine device (IUD) was associated with increased rates of PID, and led to significant concerns about the safety of IUDs in women at risk for STIs.[91] Modern IUDs, including the levonorgestrel IUD (Mirena) and the copper IUD (Paraguard), have not been associated with an increased risk of PID over the long term.[92] There does appear to be a slightly increased rate of PID in the 20 days after insertion: in one study the rate of PID during this time was 9.66 per 1000 women, in comparison with 1.38 per 1000 women thereafter.[93] A review of studies assessing PID after IUD insertion in the presence of gonococcal or chlamydial cervicitis showed an increased, but overall low risk (0%–5%).[94] Recent studies suggest that screening for gonorrhea and chlamydia at the time of insertion, as opposed to requiring a negative test before the procedure, does not significantly increase adverse sequelae.[95] There does not appear to be any difference in the risk for PID between hormone-containing and copper IUDs.[96] The presence of an IUD at the time of diagnosis of acute PID does not alter the management, and empiric removal of the IUD is not indicated.[67,97]

SEQUELAE

Women with PID have an increased risk of ectopic pregnancy, infertility, and chronic pelvic pain caused by tubal scarring and damage from inflammation. In the PEACH

trial, 36% of participants reported chronic pelvic pain; women with 2 or more episodes of PID were at highest risk.[98] In a cohort study of women with laparoscopically confirmed salpingitis in Sweden, followed for a mean of 94 months, the infertility rate was 16%, 67% of which was attributable to tubal factor infertility, compared with an infertility rate of 2.7% in women without salpingitis. Of women who became pregnant, 9% of women with salpingitis had an ectopic pregnancy, compared with 1.9% of control women.[21] The risk of infertility increased with severity of salpingitis and number of episodes of PID. Chlamydial cervicitis also increases the risk of ectopic pregnancy with repeat infections; women with 3 or more episodes had 4.5 times increased odds of PID.[21]

In the PEACH trial, upper genital tract detection of gonorrhea, chlamydia, or endometritis was sufficient to confirm the diagnosis of PID. However, there were no differences in reproductive health outcomes between women with and without endometritis or upper genital tract infection.[42] A more recent study of women with lower genital tract infection but no PID by clinical criteria used a permissive definition of endometritis (1 plasma cell per high-power field) and showed a 40% decrease in pregnancy rates among women with endometritis (or subclinical PID).[44] The differences in these analyses may be due to a slightly higher rate of *C trachomatis* infection in the latter study.

PREVENTION

As gonorrhea and chlamydia contribute more than half to three-quarters of PID, screening for and treating these infections should decrease the incidence and sequelae. Four randomized trials have examined whether this strategy is effective. The earliest was conducted between 1990 and 1992 in Seattle, Washington. More than 1000 women in a managed care organization were randomized to receive an invitation for chlamydia screening, then followed for a year and compared with approximately 1600 women receiving standard care. Although only 64% of the intervention group were screened, during the 12-month follow-up there were 9 PID cases in the screening group and 33 in the control group (relative risk 0.44, 95% confidence interval 0.2–0.9).[99] A second study used cluster randomization to randomize students at 17 high schools to receive the offer of chlamydia screening, then followed them for PID over 12 months. At 1 year the PID incidence was 2.1% in the screening group (of whom 48% were screened) and 4.2% in the control group.[100] Most recently, the Prevention Of Pelvic Infections (POPI) trial in England enrolled sexually active women younger than 27 years and randomized them to early versus delayed screening for chlamydia. The early screening group had a chlamydia prevalence of 5.4%, and 15 of 1191 (1.3%) developed PID over the course of the study. In the delayed group, 5.9% had chlamydia detected on their enrollment swab when it was tested a year later. During that time, 23 of 1186 (1.9%) in this group developed PID. The relative risk for PID in those with early screening was not significant (0.65; 95% confidence interval 0.34–1.22),[32] but the study was underpowered given the low rate of PID.

SUMMARY

PID is associated with significant reproductive morbidity, which appears to be reduced with prompt, proactive treatment of cervicitis and lower genital tract infections. It is a clinical diagnosis, and providers should maintain a high index of suspicion when presented with a woman of reproductive age complaining of abdominal and pelvic pain. STIs are commonly associated with PID, but vaginal anaerobes also seem to be

involved, and antibiotic coverage for these pathogens should be considered when treating women with severe symptoms or pelvic abscesses.

REFERENCES

1. Rein DB, Kassler WJ, Irwin KL, et al. Direct medical cost of pelvic inflammatory disease and its sequelae: decreasing, but still substantial. Obstet Gynecol 2000;95(3):397–402.
2. Bender N, Herrmann B, Andersen B, et al. Chlamydia infection, pelvic inflammatory disease, ectopic pregnancy and infertility: cross-national study. Sex Transm Infect 2011;87(7):601–8.
3. Paik CK, Waetjen LE, Xing G, et al. Hospitalizations for pelvic inflammatory disease and tuboovarian abscess. Obstet Gynecol 2006;107(3):611–6.
4. Sutton MY, Sternberg M, Zaidi A, et al. Trends in pelvic inflammatory disease hospital discharges and ambulatory visits, United States, 1985-2001. Sex Transm Dis 2005;32(12):778–84.
5. Owusu-Edusei K Jr, Bohm MK, Chesson HW, et al. Chlamydia screening and pelvic inflammatory disease: insights from exploratory time-series analyses. Am J Prev Med 2010;38(6):652–7.
6. Bohm MK, Newman L, Satterwhite CL, et al. Pelvic inflammatory disease among privately insured women, United States, 2001-2005. Sex Transm Dis 2010;37(3):131–6.
7. Ness RB, Soper DE, Holley RL, et al. Hormonal and barrier contraception and risk of upper genital tract disease in the PID Evaluation and Clinical Health (PEACH) study. Am J Obstet Gynecol 2001;185(1):121–7.
8. Ness RB, Soper DE, Holley RL, et al. Douching and endometritis: results from the PID Evaluation and Clinical Health (PEACH) study. Sex Transm Dis 2001;28(4):240–5.
9. Simms I, Stephenson JM, Mallinson H, et al. Risk factors associated with pelvic inflammatory disease. Sex Transm Infect 2006;82(6):452–7.
10. Scholes D, Daling JR, Stergachis A, et al. Vaginal douching as a risk factor for acute pelvic inflammatory disease. Obstet Gynecol 1993;81(4):601–6.
11. Wolner-Hanssen P, Eschenbach DA, Paavonen J, et al. Association between vaginal douching and acute pelvic inflammatory disease. JAMA 1990;263(14):1936–41.
12. Kimani J, Maclean IW, Bwayo JJ, et al. Risk factors for *Chlamydia trachomatis* pelvic inflammatory disease among sex workers in Nairobi, Kenya. J Infect Dis 1996;173(6):1437–44.
13. Ness RB, Keder LM, Soper DE, et al. Oral contraception and the recognition of endometritis. Am J Obstet Gynecol 1997;176(3):580–5.
14. Wolner-Hanssen P, Svensson L, Mardh PA, et al. Laparoscopic findings and contraceptive use in women with signs and symptoms suggestive of acute salpingitis. Obstet Gynecol 1985;66(2):233–8.
15. Taylor BD, Darville T, Haggerty CL. Does bacterial vaginosis cause pelvic inflammatory disease? Sex Transm Dis 2013;40(2):117–22.
16. Ness RB, Hillier SL, Kip KE, et al. Bacterial vaginosis and risk of pelvic inflammatory disease. Obstet Gynecol 2004;104(4):761–9.
17. Eschenbach DA, Buchanan TM, Pollock HM, et al. Polymicrobial etiology of acute pelvic inflammatory disease. N Engl J Med 1975;293(4):166–71.
18. Sweet RL. Pelvic inflammatory disease. Sex Transm Dis 1986;13(Suppl 3):192–8.

19. Taylor BD, Ness RB, Darville T, et al. Microbial correlates of delayed care for pelvic inflammatory disease. Sex Transm Dis 2011;38(5):434–8.
20. Haggerty CL, Totten PA, Astete SG, et al. *Mycoplasma genitalium* among women with nongonococcal, nonchlamydial pelvic inflammatory disease. Infect Dis Obstet Gynecol 2006;2006:30184.
21. Westrom L, Joesoef R, Reynolds G, et al. Pelvic inflammatory disease and fertility. A cohort study of 1,844 women with laparoscopically verified disease and 657 control women with normal laparoscopic results. Sex Transm Dis 1992;19(4):185–92.
22. Heinonen PK, Miettinen A. Laparoscopic study on the microbiology and severity of acute pelvic inflammatory disease. Eur J Obstet Gynecol Reprod Biol 1994; 57(2):85–9.
23. Hillier SL, Kiviat NB, Hawes SE, et al. Role of bacterial vaginosis-associated microorganisms in endometritis. Am J Obstet Gynecol 1996;175(2):435–41.
24. Taylor-Robinson D, Jensen JS, Svenstrup H, et al. Difficulties experienced in defining the microbial cause of pelvic inflammatory disease. Int J STD AIDS 2012;23(1):18–24.
25. Bjartling C, Osser S, Persson K. *Mycoplasma genitalium* in cervicitis and pelvic inflammatory disease among women at a gynecologic outpatient service. Am J Obstet Gynecol 2012;206(6):476.e1–8.
26. Cohen CR, Manhart LE, Bukusi EA, et al. Association between *Mycoplasma genitalium* and acute endometritis. Lancet 2002;359(9308):765–6.
27. Soper DE, Brockwell NJ, Dalton HP, et al. Observations concerning the microbial etiology of acute salpingitis. Am J Obstet Gynecol 1994;170(4):1008–14 [discussion: 14–7].
28. Wasserheit JN, Bell TA, Kiviat NB, et al. Microbial causes of proven pelvic inflammatory disease and efficacy of clindamycin and tobramycin. Ann Intern Med 1986;104(2):187–93.
29. Hebb JK, Cohen CR, Astete SG, et al. Detection of novel organisms associated with salpingitis, by use of 16S rRNA polymerase chain reaction. J Infect Dis 2004;190(12):2109–20.
30. Herzog SA, Althaus CL, Heijne JC, et al. Timing of progression from *Chlamydia trachomatis* infection to pelvic inflammatory disease: a mathematical modelling study. BMC Infect Dis 2012;12:187.
31. Morre SA, van den Brule AJ, Rozendaal L, et al. The natural course of asymptomatic *Chlamydia trachomatis* infections: 45% clearance and no development of clinical PID after one-year follow-up. Int J STD AIDS 2002; 13(Suppl 2):12–8.
32. Oakeshott P, Kerry S, Aghaizu A, et al. Randomised controlled trial of screening for *Chlamydia trachomatis* to prevent pelvic inflammatory disease: the POPI (Prevention of Pelvic Infection) trial. BMJ 2010;340:c1642.
33. Katz DF. Human cervical mucus: research update. Am J Obstet Gynecol 1991; 165(6 Pt 2):1984–6.
34. Kunz G, Beil D, Deininger H, et al. The dynamics of rapid sperm transport through the female genital tract: evidence from vaginal sonography of uterine peristalsis and hysterosalpingoscintigraphy. Hum Reprod 1996;11(3):627–32.
35. Darville T, Hiltke TJ. Pathogenesis of genital tract disease due to *Chlamydia trachomatis*. J Infect Dis 2010;201(Suppl 2):S114–25.
36. Patton DL, Kuo CC. Histopathology of *Chlamydia trachomatis* salpingitis after primary and repeated reinfections in the monkey subcutaneous pocket model. J Reprod Fertil 1989;85(2):647–56.

37. Van Voorhis WC, Barrett LK, Sweeney YT, et al. Repeated *Chlamydia trachomatis* infection of *Macaca nemestrina* fallopian tubes produces a th1-like cytokine response associated with fibrosis and scarring. Infect Immun 1997;65(6):2175–82.
38. Peeling RW, Kimani J, Plummer F, et al. Antibody to chlamydial hsp60 predicts an increased risk for chlamydial pelvic inflammatory disease. J Infect Dis 1997;175(5):1153–8.
39. Toye B, Laferriere C, Claman P, et al. Association between antibody to the chlamydial heat-shock protein and tubal infertility. J Infect Dis 1993;168(5):1236–40.
40. Ness RB, Soper DE, Richter HE, et al. Chlamydia antibodies, chlamydia heat shock protein, and adverse sequelae after pelvic inflammatory disease: the PID Evaluation and Clinical Health (PEACH) study. Sex Transm Dis 2008;35(2):129–35.
41. Kiviat NB, Wolner-Hanssen P, Eschenbach DA, et al. Endometrial histopathology in patients with culture-proved upper genital tract infection and laparoscopically diagnosed acute salpingitis. Am J Surg Pathol 1990;14(2):167–75.
42. Haggerty CL, Ness RB, Amortegui A, et al. Endometritis does not predict reproductive morbidity after pelvic inflammatory disease. Am J Obstet Gynecol 2003;188(1):141–8.
43. Achilles SL, Amortegui AJ, Wiesenfeld HC. Endometrial plasma cells: do they indicate subclinical pelvic inflammatory disease? Sex Transm Dis 2005;32(3):185–8.
44. Wiesenfeld HC, Hillier SL, Meyn LA, et al. Subclinical pelvic inflammatory disease and infertility. Obstet Gynecol 2012;120(1):37–43.
45. Jacobson L. Differential diagnosis of acute pelvic inflammatory disease. Am J Obstet Gynecol 1980;138(7 Pt 2):1006–11.
46. Short VL, Totten PA, Ness RB, et al. Clinical presentation of *Mycoplasma genitalium* infection versus *Neisseria gonorrhoeae* infection among women with pelvic inflammatory disease. Clin Infect Dis 2009;48(1):41–7.
47. Jacobson L, Westrom L. Objectivized diagnosis of acute pelvic inflammatory disease. Diagnostic and prognostic value of routine laparoscopy. Am J Obstet Gynecol 1969;105(7):1088–98.
48. Simms I, Eastick K, Mallinson H, et al. Associations between *Mycoplasma genitalium*, *Chlamydia trachomatis*, and pelvic inflammatory disease. Sex Transm Infect 2003;79(2):154–6.
49. Eckert LO, Hawes SE, Wolner-Hanssen PK, et al. Endometritis: the clinical-pathologic syndrome. Am J Obstet Gynecol 2002;186(4):690–5.
50. Paavonen J, Kiviat N, Brunham RC, et al. Prevalence and manifestations of endometritis among women with cervicitis. Am J Obstet Gynecol 1985;152(3):280–6.
51. Kahn JG, Walker CK, Washington AE, et al. Diagnosing pelvic inflammatory disease. A comprehensive analysis and considerations for developing a new model. JAMA 1991;266(18):2594–604.
52. Peipert JF, Ness RB, Blume J, et al. Clinical predictors of endometritis in women with symptoms and signs of pelvic inflammatory disease. Am J Obstet Gynecol 2001;184(5):856–63 [discussion: 63–4].
53. Yudin MH, Hillier SL, Wiesenfeld HC, et al. Vaginal polymorphonuclear leukocytes and bacterial vaginosis as markers for histologic endometritis among women without symptoms of pelvic inflammatory disease. Am J Obstet Gynecol 2003;188(2):318–23.
54. Peipert JF, Boardman L, Hogan JW, et al. Laboratory evaluation of acute upper genital tract infection. Obstet Gynecol 1996;87(5 Pt 1):730–6.

55. Cacciatore B, Leminen A, Ingman-Friberg S, et al. Transvaginal sonographic findings in ambulatory patients with suspected pelvic inflammatory disease. Obstet Gynecol 1992;80(6):912–6.
56. Timor-Tritsch IE, Lerner JP, Monteagudo A, et al. Transvaginal sonographic markers of tubal inflammatory disease. Ultrasound Obstet Gynecol 1998; 12(1):56–66.
57. Molander P, Finne P, Sjoberg J, et al. Observer agreement with laparoscopic diagnosis of pelvic inflammatory disease using photographs. Obstet Gynecol 2003;101(5 Pt 1):875–80.
58. Tukeva TA, Aronen HJ, Karjalainen PT, et al. MR imaging in pelvic inflammatory disease: comparison with laparoscopy and us. Radiology 1999;210(1): 209–16.
59. Wolner-Hanssen P, Paavonen J, Kiviat N, et al. Outpatient treatment of pelvic inflammatory disease with cefoxitin and doxycycline. Obstet Gynecol 1988;71(4): 595–600.
60. Arredondo JL, Diaz V, Gaitan H, et al. Oral clindamycin and ciprofloxacin versus intramuscular ceftriaxone and oral doxycycline in the treatment of mild-to-moderate pelvic inflammatory disease in outpatients. Clin Infect Dis 1997; 24(2):170–8.
61. Ness RB, Soper DE, Holley RL, et al. Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease: results from the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) randomized trial. Am J Obstet Gynecol 2002;186(5):929–37.
62. Ness RB, Trautmann G, Richter HE, et al. Effectiveness of treatment strategies of some women with pelvic inflammatory disease: a randomized trial. Obstet Gynecol 2005;106(3):573–80.
63. Dunbar-Jacob J, Sereika SM, Foley SM, et al. Adherence to oral therapies in pelvic inflammatory disease. J Womens Health (Larchmt) 2004;13(3):285–91.
64. Augenbraun MH, McCormack WH. Pelvic inflammatory disease: an ongoing epidemic. Hosp Pract (1995) 1995;30(9):61–6.
65. Katz BP, Zwickl BW, Caine VA, et al. Compliance with antibiotic therapy for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Sex Transm Dis 1992; 19(6):351–4.
66. Hemsell DL, Little BB, Faro S, et al. Comparison of three regimens recommended by the centers for disease control and prevention for the treatment of women hospitalized with acute pelvic inflammatory disease. Clin Infect Dis 1994;19(4):720–7.
67. Workowski KA, Berman S. Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 2010;59(RR-12):1–110.
68. Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. MMWR Recomm Rep 2006;55(RR-11):1–94.
69. Katz AR, Lee MV, Wasserman GM. Sexually transmitted disease (STD) update: a review of the CDC 2010 STD treatment guidelines and epidemiologic trends of common STDs in Hawai'i. Hawaii J Med Public Health 2012;71(3):68–73.
70. Bevan CD, Ridgway GL, Rothermel CD. Efficacy and safety of azithromycin as monotherapy or combined with metronidazole compared with two standard multidrug regimens for the treatment of acute pelvic inflammatory disease. J Int Med Res 2003;31(1):45–54.
71. Savaris RF, Teixeira LM, Torres TG, et al. Comparing ceftriaxone plus azithromycin or doxycycline for pelvic inflammatory disease: a randomized controlled trial. Obstet Gynecol 2007;110(1):53–60.

72. Haggerty CL, Totten PA, Astete SG, et al. Failure of cefoxitin and doxycycline to eradicate endometrial *Mycoplasma genitalium* and the consequence for clinical cure of pelvic inflammatory disease. Sex Transm Infect 2008;84(5):338–42.
73. Manhart LE, Broad JM, Golden MR. *Mycoplasma genitalium*: should we treat and how? Clin Infect Dis 2011;53(Suppl 3):S129–42.
74. Haggerty CL, Hillier SL, Bass DC, et al. Bacterial vaginosis and anaerobic bacteria are associated with endometritis. Clin Infect Dis 2004;39(7):990–5.
75. Swidsinski A, Verstraelen H, Loening-Baucke V, et al. Presence of a polymicrobial endometrial biofilm in patients with bacterial vaginosis. PLoS One 2013; 8(1):e53997.
76. Walker CK, Workowski KA, Washington AE, et al. Anaerobes in pelvic inflammatory disease: implications for the centers for disease control and prevention's guidelines for treatment of sexually transmitted diseases. Clin Infect Dis 1999; 28(Suppl 1):S29–36.
77. Landers DV, Sweet RL. Tubo-ovarian abscess: contemporary approach to management. Rev Infect Dis 1983;5(5):876–84.
78. Reed SD, Landers DV, Sweet RL. Antibiotic treatment of tuboovarian abscess: comparison of broad-spectrum beta-lactam agents versus clindamycin-containing regimens. Am J Obstet Gynecol 1991;164(6 Pt 1):1556–61 [discussion: 61–2].
79. Gjelland K, Ekerhovd E, Granberg S. Transvaginal ultrasound-guided aspiration for treatment of tubo-ovarian abscess: a study of 302 cases. Am J Obstet Gynecol 2005;193(4):1323–30.
80. Goharkhay N, Verma U, Maggiorotto F. Comparison of CT- or ultrasound-guided drainage with concomitant intravenous antibiotics vs. intravenous antibiotics alone in the management of tubo-ovarian abscesses. Ultrasound Obstet Gynecol 2007;29(1):65–9.
81. Irwin KL, Moorman AC, O'Sullivan MJ, et al. Influence of human immunodeficiency virus infection on pelvic inflammatory disease. Obstet Gynecol 2000; 95(4):525–34.
82. Korn AP, Landers DV, Green JR, et al. Pelvic inflammatory disease in human immunodeficiency virus-infected women. Obstet Gynecol 1993;82(5):765–8.
83. Cohen CR, Sinei S, Reilly M, et al. Effect of human immunodeficiency virus type 1 infection upon acute salpingitis: a laparoscopic study. J Infect Dis 1998; 178(5):1352–8.
84. Kamenga MC, De Cock KM, St Louis ME, et al. The impact of human immunodeficiency virus infection on pelvic inflammatory disease: a case-control study in Abidjan, Ivory Coast. Am J Obstet Gynecol 1995;172(3):919–25.
85. Mugo NR, Kiehlbauch JA, Nguti R, et al. Effect of human immunodeficiency virus-1 infection on treatment outcome of acute salpingitis. Obstet Gynecol 2006;107(4):807–12.
86. Bukusi EA, Cohen CR, Stevens CE, et al. Effects of human immunodeficiency virus 1 infection on microbial origins of pelvic inflammatory disease and on efficacy of ambulatory oral therapy. Am J Obstet Gynecol 1999;181(6):1374–81.
87. Heaton FC, Ledger WJ. Postmenopausal tuboovarian abscess. Obstet Gynecol 1976;47(1):90–4.
88. Protopapas AG, Diakomanolis ES, Milingos SD, et al. Tubo-ovarian abscesses in postmenopausal women: gynecological malignancy until proven otherwise? Eur J Obstet Gynecol Reprod Biol 2004;114(2):203–9.
89. Lipscomb GH, Ling FW. Tubo-ovarian abscess in postmenopausal patients. South Med J 1992;85(7):696–9.

90. Hoffman M, Molpus K, Roberts WS, et al. Tuboovarian abscess in postmenopausal women. J Reprod Med 1990;35(5):525–8.
91. Gareen IF, Greenland S, Morgenstern H. Intrauterine devices and pelvic inflammatory disease: meta-analyses of published studies, 1974-1990. Epidemiology 2000;11(5):589–97.
92. Feldblum PJ, Caraway J, Bahamondes L, et al. Randomized assignment to copper IUD or depot-medroxyprogesterone acetate: feasibility of enrollment, continuation and disease ascertainment. Contraception 2005;72(3):187–91.
93. Farley TM, Rosenberg MJ, Rowe PJ, et al. Intrauterine devices and pelvic inflammatory disease: an international perspective. Lancet 1992;339(8796):785–8.
94. Mohllajee AP, Curtis KM, Peterson HB. Does insertion and use of an intrauterine device increase the risk of pelvic inflammatory disease among women with sexually transmitted infection? A systematic review. Contraception 2006;73(2):145–53.
95. Sufrin CB, Postlethwaite D, Armstrong MA, et al. *Neisseria gonorrhoeae* and *Chlamydia trachomatis* screening at intrauterine device insertion and pelvic inflammatory disease. Obstet Gynecol 2012;120(6):1314–21.
96. Sivin I, Stern J, Diaz J, et al. Two years of intrauterine contraception with levonorgestrel and with copper: a randomized comparison of the TCU 380ag and levonorgestrel 20 mcg/day devices. Contraception 1987;35(3):245–55.
97. Soderberg G, Lindgren S. Influence of an intrauterine device on the course of an acute salpingitis. Contraception 1981;24(2):137–43.
98. Haggerty CL, Peipert JF, Weitzen S, et al. Predictors of chronic pelvic pain in an urban population of women with symptoms and signs of pelvic inflammatory disease. Sex Transm Dis 2005;32(5):293–9.
99. Scholes D, Stergachis A, Heidrich FE, et al. Prevention of pelvic inflammatory disease by screening for cervical chlamydial infection. N Engl J Med 1996;334(21):1362–6.
100. Ostergaard L, Andersen B, Moller JK, et al. Home sampling versus conventional swab sampling for screening of *Chlamydia trachomatis* in women: a cluster-randomized 1-year follow-up study. Clin Infect Dis 2000;31(4):951–7.
101. Marrazzo JM, Martin DH. Management of women with cervicitis. Clin Infect Dis 2007;44(Suppl 3):S102–10.
102. Paavonen J, Aine R, Teisala K, et al. Comparison of endometrial biopsy and peritoneal fluid cytologic testing with laparoscopy in the diagnosis of acute pelvic inflammatory disease. Am J Obstet Gynecol 1985;151(5):645–50.
103. Walker CK, Landers DV, Ohm-Smith MJ, et al. Comparison of cefotetan plus doxycycline with cefoxitin plus doxycycline in the inpatient treatment of acute salpingitis. Sex Transm Dis 1991;18(2):119–23.
104. Comparative evaluation of clindamycin/gentamicin and cefoxitin/doxycycline for treatment of pelvic inflammatory disease: a multi-center trial. The European Study Group. Acta Obstet Gynecol Scand 1992;71(2):129–34.
105. McGregor JA, Crombleholme WR, Newton E, et al. Randomized comparison of ampicillin-sulbactam to cefoxitin and doxycycline or clindamycin and gentamicin in the treatment of pelvic inflammatory disease or endometritis. Obstet Gynecol 1994;83(6):998–1004.
106. Walters MD, Gibbs RS. A randomized comparison of gentamicin-clindamycin and cefoxitin-doxycycline in the treatment of acute pelvic inflammatory disease. Obstet Gynecol 1990;75(5):867–72.
107. Piyadigamage A, Wilson J. Improvement in the clinical cure rate of outpatient management of pelvic inflammatory disease following a change in therapy. Sex Transm Infect 2005;81(3):233–5.