

Pelvic inflammatory disease: improving awareness, prevention, and treatment

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Purpose: Pelvic inflammatory disease (PID) is a common disorder of the reproductive tract that is frequently misdiagnosed and inadequately treated. PID and its complications, such as infertility, ectopic pregnancy, and chronic pelvic pain, are preventable by screening asymptomatic patients for sexually transmitted infections (STIs) and promptly treating individuals with STIs and PID.

Recent findings: The rates of adverse outcomes in women with PID are high and disproportionately affect young minority women. There are key opportunities for prevention including improving provider adherence with national screening guidelines for STIs and PID treatment recommendations and patient medication adherence. Nearly half of all eligible women are not screened for STIs according to national quality standards, which may increase the risk of both acute and subclinical PID. Moreover, in clinical practice, providers poorly adhere to the Centers for Disease Control and Prevention recommendations for treatment of PID. Additionally, patients with PID struggle to adhere to the current management strategies in the outpatient setting.

Conclusion: Novel evidence-based clinical and public health interventions to further reduce the rates of PID and to improve outcomes for affected women are warranted. We propose potential cost-effective approaches that could be employed in real-world settings.

Keywords: pelvic inflammatory disease, treatment, disparities

Introduction

In the US, ~800,000 women are diagnosed with pelvic inflammatory disease (PID) each year.¹ However, the US Centers for Disease Control and Prevention (CDC) estimates that more than one million women experience an episode of PID each year taking into account missed cases of PID.² The rates of PID are concerning given the serious potential sequelae of PID, including tubal infertility, ectopic pregnancy, and chronic pelvic pain (CPP). Missed and/or improperly or inadequately treated cases of PID increase the risk of complications of PID.³ Not only does the severity of these complications highlight the seriousness of the disorder, but also young women indicated that they are willing to give up 1–2 years of their life to prevent PID and its associated sequelae, as reported in a recent health economics study using time trade offs to assess patient utilities for the health states associated with PID in a general population sample.⁴

PID is an infection of the female upper reproductive tract, including the endometrium, fallopian tubes, ovaries, and pelvic peritoneum.⁵ Sexually transmitted infections (STIs), such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, are commonly implicated in cases of PID, but they are not the only organisms associated with clinical disease. The diagnosis of PID is made difficult by variation in clinical manifestations: subclinical patients with PID are asymptomatic, while patients with more severe disease

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present with abdominal pain requiring surgical intervention.^{6,7} Subclinical PID is defined as inflammation of the upper reproductive tract in the absence of signs and symptoms of acute PID.⁷ According to the CDC 2015 Sexually Transmitted Diseases Treatment Guidelines, any young sexually active woman or woman at risk for STIs with unexplained lower abdominal or pelvic pain and at least one of the following clinical criteria noted on pelvic examination should receive presumptive treatment for PID: cervical motion tenderness, uterine tenderness, and adnexal tenderness (Table 1).⁸ In this review, we aim to discuss the current state of PID management and propose new strategies for optimal management.

Awareness

Data from the National Survey of Family Growth (NSFG) from 2006 to 2010 showed that 5.0% of women reported being treated for PID in their lifetime.⁹ Using secondary analysis of data from the PID Evaluation and Clinical Health (PEACH) study (a multicenter, randomized control trial designed to compare outpatient and inpatient treatment regimens in women with PID⁷) conducted by Trent et al,¹⁰ reported that 7 years after a diagnosis of PID, 21.3% of women experienced recurrent PID, 19.0% developed infertility, and 42.7% of women reported having CPP. The study of PID in younger populations has revealed that adolescents are at even greater risk of developing PID and associated complications. An estimated one in five cases of PID occur in women younger than 19 years, and in one study, adolescents and young women aged 17–21 years were twice as likely as other age groups to be diagnosed with PID.^{11,12} The increased risk of PID in adolescents is thought to be secondary to a combination of behavioral and biological factors.¹³ In terms of behavioral risk, adolescents are likely to have multiple

sex partners, engage in unprotected sex, and have short duration and high frequency monogamous relationships.¹⁴ Biologically, adolescents have a greater proportion of surface area for microorganisms to infect.^{13,15} Trent et al also found in the PEACH study that adolescents aged ≤19 years with recurrent PID were five times more likely to report CPP 7 years after being diagnosed with PID. Additionally, adolescents in the PEACH study developed recurrent PID in a shorter period of time than adult women.¹⁰

There are also significant health disparities associated with PID.^{16–21} Sutton et al¹ found that the rates of PID diagnosis in black women were two to three times greater than those in white women in hospital and ambulatory settings. Consistent with this racial disparity, Goyal et al¹² more recently found that race was associated with a diagnosis of PID in adolescent patients evaluated in the emergency department. Furthermore, a retrospective analysis of the NSFG from 2006 to 2010 showed that women with an income of <150% of the federal poverty level as measured by the US census²² and less than a high school education have the highest self-reported frequency of PID treatment.²³

Prevention

Prevention of PID falls broadly into the following two categories: 1) prevention of the first PID episode and 2) prevention of recurrent disease. Women who have had one episode of PID need to prevent STI infection given the relationship between recurrent STIs, such as *C. trachomatis* and infertility.²⁴ Prevention of the first episode of PID requires early diagnosis of STIs and therefore improved provider adherence to the United States Preventive Screening Task Force and CDC guidelines. In the 2015 Sexually Transmitted Diseases Treatment Guidelines, the CDC recommends

Table 1 PID diagnostic criteria per 2015 CDC guidelines

Minimal clinical criteria ^a	Cervical motion tenderness Uterine tenderness Adnexal tenderness
Additional criteria ^b	Oral temperature greater than 101 °F (38.3°C) Abnormal cervical mucopurulent discharge or cervical friability Abundant white blood cells on microscopic evaluation of vaginal fluid Elevated erythrocyte sedimentation rate Elevated C-reactive protein Laboratory documentation of cervical infection with <i>Neisseria gonorrhoeae</i> or <i>Chlamydia trachomatis</i>
Specific criteria ^c	Endometrial biopsy with histopathologic evidence of endometritis Transvaginal ultrasound or magnetic resonance imaging showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex, or Doppler studies suggesting pelvic infection Laparoscopic findings consistent with PID

Notes: Reproduced from CDC. 2015 Sexually Transmitted Diseases Treatment Guidelines. Atlanta, GA: Department of Health and Human Services; 2015.³ ^aInitiate treatment if one or more of these criteria are met. ^bIn addition to one or more minimal criteria, one or more of the additional criteria increases specificity of the diagnosis of PID. ^cOne or more of these criteria provides the most specific diagnosis of PID.

Abbreviations: CDC, US Centers for Disease Control and Prevention; PID, pelvic inflammatory disease.

annual chlamydia and gonorrhea screening in all sexually active women younger than 25 years of age and in sexually active women 25 years of age and older at increased risk defined as women who have a new sex partner, those who have more than one sex partner, those whose sex partner has concurrent partners, or those with a sex partner who has an STI.²⁵ The CDC also recommends considering regular screening for *Trichomonas vaginalis* in women receiving care in high STI prevalence settings and women engaged in high risk behaviors, such as sex with multiple partners, exchanging sex for money or drugs, use of illicit drugs, and prior history of an STI. Women who test positive for an STI should be rescreened for STIs 3 months after STI treatment, particularly if they reside in STI-prevalent communities and/or new behavioral risks are identified at the follow-up visit.⁸ Randomized control trials of women diagnosed with *C. trachomatis* suggest that screening can lead to a reduction in PID incidence.^{26,27} Unfortunately, physicians have largely failed to screen eligible women according to national standards. An analysis of the NSFG from 2006 to 2010 estimates that 40% of sexually active US women aged 15–21 years were screened for *C. trachomatis*.²⁸ Additional concern is raised for newly recognized STIs, such as *Mycoplasma genitalium*, for which commercial testing is not yet available in the US. Several studies have demonstrated that both *T. vaginalis* and *M. genitalium* are associated with PID.^{29,30} Not only does failure of asymptomatic STI screening lead to inadvertent spreading of and increasing the national burden of STIs, but also untreated STIs predispose women to PID.

Screening and early treatment of STIs can also decrease the incidence of subclinical PID, which has similar morbidity to acute PID. The exact incidence of subclinical PID is difficult to determine, but studies have suggested that incidence is high. In a cross-sectional study, using endometrial biopsies of

women diagnosed with or at risk for STIs in clinical settings, Wiesenfeld et al³¹ detected subclinical PID in 26% of women with *Neisseria gonorrhoeae* and 27% of women with *C. trachomatis*. Biopsy specimens demonstrate that subclinical PID may be as destructive to fallopian tubes as acute symptomatic PID³² and is also associated with infertility.⁷ Given that subclinical PID lacks overt clinical signs and symptoms, asymptomatic STI screening and early treatment are critical.

Prevention of recurrent PID is also a public health priority. It is well established that patients with recurrent PID are at risk for greater reproductive sequelae than those who avoid subsequent disease. Using a Scandinavian inpatient cohort of patients diagnosed with PID between 1960 and 1984, Weström et al³³ found that infertility roughly doubles with each subsequent episode of PID. Similarly, using data from the PEACH study, Trent et al¹⁰ found that women with recurrent PID were almost two times more likely to report infertility and over four times more likely to report CPP.

Among women with PID, recurrent disease is not uncommon. Data from the PEACH study shows that <3 years after initial PID diagnosis, 14.5% of participants had recurrent PID, and at 7 years, >21% had repeat PID.³⁴ These data suggest that additional efforts to implement clinical interventions aimed at adequate treatment and prevention of recurrent disease are warranted.

Treatment

Damage to the female reproductive tract from PID is usually irreversible; therefore, prompt antibiotic treatment is necessary to prevent any scarring of the reproductive tract.³⁵ Treatment of PID per CDC guidance includes broad spectrum antibiotic coverage (Table 2). Parenteral and oral antibiotic regimens have been found to have similar efficacy in women with mild to moderately severe PID,^{36,37} and Smith et al³⁸

Table 2 PID antibiotic regimens per 2015 CDC PID treatment guidelines

Parenteral treatment ^a	
Regimen A	CeFotetan 2 g IV every 12 hours + doxycycline 100 mg PO or IV every 12 hours
Regimen B	CeFoxitin 2 g IV every 6 hours + doxycycline 100 mg PO or IV every 12 hours
Regimen C	Clindamycin 900 mg IV every 8 hours + gentamicin 2 mg/kg loading dose IV or IM followed by 1.5 mg/kg every 8 hours (can substitute single daily dosage of 3–5 mg/kg)
Alternate regimen	Ampicillin/sulbactam 3 g IV every 6 hours + doxycycline 100 mg orally or IV every 12 hours
Oral treatment	
Regimen A	CeTriaxone 250 mg IM in a single dose + doxycycline 100 mg PO BID for 14 days ± metronidazole 500 mg PO BID for 14 days
Regimen B	CeFoxitin 2 g IM and probenecid 1 g PO in a single dose + doxycycline 100 mg PO BID for 14 days ± metronidazole 500 mg PO BID for 14 days
Regimen C	A Third-generation cephalosporin + doxycycline 100 mg PO BID for 14 days ± metronidazole 500 mg PO BID for 14 days

Notes: Reproduced from CDC. 2015 Sexually Transmitted Diseases Treatment Guidelines. Atlanta, GA: Department of Health and Human Services; 2015.³ Trials have shown short-term clinical effectiveness with monotherapy azithromycin 500 mg IV daily for one or two doses +250 mg PO for 5–6 days, or combined with a 12-day course of metronidazole.^{57,58} ^aContinuation of parenteral regimens for 24 hours after clinical improvement then transition to oral regimen to complete the 14-day treatment course.

Abbreviations: BID, twice daily; CDC, US Centers for Disease Control and Prevention; IM, intramuscular; IV, intravenous; PID, pelvic inflammatory disease; PO, by mouth.

demonstrate that inpatient hospitalization for the treatment of PID is not economically feasible; therefore, the CDC recommends oral regimens in this subgroup of patients in the outpatient setting. Inpatient treatment is recommended for patients who meet any of the following criteria: 1) unable to exclude a surgical emergency, 2) tubo-ovarian abscess, 3) pregnancy, 4) severe illness (eg, nausea, vomiting, and high fever), 5) inability to tolerate outpatient regimen, and 6) failure to respond to oral regimen with persistent and/or worsening symptoms. All patients should be reevaluated by a clinician within 72 hours after initiating treatment. Additional evaluation and/or hospitalization for parenteral antibiotics may be indicated for patients who do not show clinical improvement at this time. Male sexual partners from the last 60 days should be evaluated, tested, and treated for *C. trachomatis* and *GC*.

The 72-hour visit is critically important to assess the clinical status of the patient, particularly given the rise in multidrug-resistant *N. gonorrhoeae*. The spread of cephalosporin-resistant *GC* is estimated to lead to an additional 75,000 cases of PID over a 10-year period.³⁹ These clinical scenarios are likely to be more complicated since they cannot be easily treated, further increasing the potential for reproductive health sequelae.

While the CDC no longer recommends differential treatment for adolescents,⁸ there are limited data to support the management of early and middle adolescents in the outpatient setting. The mean age of adolescents in the PEACH study cohort was 18 years (SD 1 year).³⁴ While providers struggle with the disposition plans for adolescents,⁴⁰ careful consideration of developmental status, social support, and actual ability to follow or tolerate an outpatient regimen should guide these decisions.³

Provider adherence to CDC treatment guidelines in the US is poor.⁴¹ In an analysis of quality improvement data from pediatric ambulatory settings within a single urban institution, Trent et al⁴² found that only 62% of patients received treatment according to national standards. An analysis of the National Hospital Ambulatory Medicare Care Survey data from 2000 to 2009 suggests a more dire national picture. Of 704,882 females aged 14–21 years diagnosed with PID in US emergency departments, only 37.1% were prescribed antibiotics that adhered to the CDC guidelines.⁴³ Even more concerning results were seen in an analysis by Woods et al⁴⁴ in which only 6% of subjects who met diagnosis criteria of PID were correctly treated with appropriate coverage in an outpatient setting. Woods et al⁴⁴ cite a disconnect between theoretical concepts and real-world applications and low overall knowledge of PID as causes of poor provider adherence to

CDC treatment guidelines. Two studies, however, have demonstrated that with provider education, provider adherence to CDC guidelines can improve.⁴⁵

Even when providers prescribe the regimens according to national standards, patients are unlikely to strictly adhere to the prescribed treatment regimens. In an analysis using the PEACH study data, Dunbar-Jacob et al found that on average, patients with PID in the study took only 70% of the prescribed doses of medication. More specifically, patients in the PEACH study did not take any medication on ~25% of their outpatient days and took medications twice daily as prescribed less than half of their outpatient treatment days. Additionally, the patients in the PEACH study took <17% of their doses within 11–13 hours of the previous dose for the twice daily treatment regimen.⁴⁶ Dunbar-Jacob et al⁴⁶ associate poor patient adherence with the length of the antibiotic course and frequency of dosing and suggest that shorter courses of less frequent dosing may improve adherence. In a study by Trent et al,⁴² patients reported additional reasons for low adherence to medication regimens, including vomiting, loss of medication, and being told by the primary care physician to stop because of negative cultures. Patients also have difficulty adhering to recommendations to follow-up with 72 hours of diagnosis. In a study of urban adolescents, only 10% of adolescents with PID returned for follow-up evaluations within 72 hours.⁴² After an institutional intervention in the same setting that included provider education and treatment algorithm, provision of a 14-day course of antibiotics at discharge, detailed written discharge instructions, and telephone follow-up, 61% of adolescents reported completed all doses of the medication, 67% practiced temporary abstinence, and 86% notified their partner for treatment.⁴² The authors reported that the patients' reasons for lack of follow-up included not being aware of the need to follow-up, no access to transportation, inability to get an appointment, and lack of a primary care provider.⁴²

New directions

The current state of PID management approach to treatment is highly focused on self-management in outpatient settings. The use of inpatient hospitalization is expensive and simply no longer a cost-effective strategy for all women.⁴⁷ There may be, however, alternative strategies that optimize the use of clinical services while continuing to reduce the cost of PID care delivery. Two potential strategies worth consideration include observation units (OUs) and community health nursing.

OUs are units within or adjacent to emergency departments where patients are admitted when they require additional

diagnostics or therapies, but discharge is anticipated within 24 hours.⁴⁸ The OU model has been found to have many benefits, including improved patient care, decreased hospital admissions, cost effectiveness, and improved emergency department efficiency.⁴⁹ The model of OUs has been applied to a variety of conditions, including chest pain, asthma, skin infections, and allergic reactions, and has been shown to be effective in several studies.^{50–53} OUs are increasingly being recognized as effective treatment strategies, and the use of observation status by Medicare beneficiaries increased by 26% from 2006 to 2008.⁵⁴ In order to reimburse for OU care, the Centers for Medicare and Medicaid Services require an observation time of at least 8 hours,⁵⁵ with a maximum of 48 hours in most circumstances.⁵⁶ OUs have been shown to be effective in both the pediatric and adult populations. Lane et al⁵⁷ performed a retrospective review of 853 patients younger than 18 years admitted for skin and soft tissue infection treatment to an OU from the emergency department between January 2003 and June 2009. Seventy percent had successful OU discharge within 26 hours. Similarly, in a randomized clinical trial of 222 patients with asthma aged 18–55 years comparing treatment outcomes in an OU and an inpatient setting, similar patients treated in an OU had asthma relapse and other morbidity rates at 8 weeks equivalent to that of patients treated with standard inpatient therapy, and cost, patient satisfaction, and quality of life outcomes favored the OU approach.⁵⁸ OU has been an effective model for a variety of conditions in both the pediatric and adult populations, including infectious disease, which suggests that this treatment model holds promise for the management of PID. In regard to PID, OUs are likely to be more cost effective than inpatient hospitalization and could allow for significant benefits regarding medication administration, consultation, patient education, and risk reduction counseling for prevention of recurrent disease. Observing patients during a short 12-hour period allows for two medication doses to be delivered, adequate counseling, mobilization of support, and assistance with prescription filling in large institutional settings. Given the increased length of stay over the emergency department for PID care, the patient's visit would likely overlap in time with the daytime staff allowing for greater access to resources, such as social work services, HIV counseling and testing, and risk reduction counseling services. However, clinical care in OUs should be time efficient because longer clinical encounters are associated with a decline in subsequent medication adherence. In a study of adolescents treated for PID in the emergency department, Hill et al⁵⁹ found that patients with above average length of service were significantly less adherent with their PID medications than patients with less

than average length of service. Health service research is needed to evaluate the effectiveness of utilizing OUs for treatment of PID with concurrent cost analyses.

Another promising strategy to facilitate self-care patients with PID is community health nursing. Community health nursing has been found to be an effective risk reduction strategy in minority and low income adolescents.^{60–65} This strategy is most well-studied in the field of maternal child health. Community health nursing is associated with decreased rates of premature birth,^{60,62} cesarean sections,⁶¹ pregnancy-induced hypertension,⁶² longer infant hospitalizations,⁶¹ child injuries,⁶² and greater resource utilization and prenatal care visit attendance.⁶³ Community health nursing has also shown promise in the field of STIs and HIV. Preliminary data from the Technology-Enhanced Community Health Nursing study have demonstrated that community health nursing combined with text messaging support is both feasible and acceptable for use in urban adolescents with PID.⁶⁵ The program utilizes the Sister to Sister intervention,⁶⁶ a CDC-approved evidence-based intervention along with text delivery of the 72 hours intervention by a trained community health nurse and text messaging support during the 14-day treatment period. While promising, research is ongoing to evaluate the impact of the intervention delivered by community health nurses on recurrent STIs after PID.

An additional gap in current PID prevention and treatment is the notification and treatment of male sexual partners. As mentioned earlier, recurrent PID is not uncommon and is associated with significant reproductive sequelae. If treatment efforts are focused solely on females, male sexual partners will continue to propagate infections. Both strategies that we propose, OUs and community health nurses, include risk reduction counseling, which includes counseling of females with PID on the importance of notifying their male sexual partners and referring them to treatment. Trent et al⁴² have shown that in pediatric ambulatory settings, an intervention, including nurse telephone follow-up at 24–48 hours and 2 weeks following discharge with PID diagnosis, was associated with high rates of partner notification and partner receipt of treatment. Additional research will need to be conducted to evaluate the effects of risk reduction counseling on male partner notification and treatment.

Conclusion

This review of the literature has identified the need for more vigilant screening for asymptomatic STIs in eligible female patients in order to prevent PID through early treatment of STIs with the goal of preventing damage to the reproductive tract that predisposes patients to infertility, ectopic pregnancy,

and CPP. Importantly, behavioral interventions designed to improve provider and patient adherence to CDC treatment guidelines work, but must be widely implemented for improvement in population outcomes. The authors postulate that established interventions, such as OUs and community health nursing, used in new ways have promise for improving patient outcomes after PID.

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