Review Article

Acute pelvic inflammatory disease

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Abstract: Pelvic inflammatory disease (PID) is an upper genital tract infection in females that is typically acquired via sexual activity. It usually is initiated by the presence of *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae* and escalates into a polymicrobial infection from local genital tract flora. Research identifies various known risk factors including young age, immunopathology and others. This article reviews the epidemiology, differential diagnosis, management, and concepts of prevention for PID.

Keywords: Pelvic inflammatory disease (PID); genital infection; sexually transmitted disease (STD); adolescents; sexual activity

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Introduction

Pelvic inflammatory disease (PID) is a major sexually transmitted disease typically involving sexually active adolescent and young adult females (1). Its presentation can be confusing with an extensive differential diagnosis. This discussion considers principles of PID management based on guidelines from the United States Centers for Disease Control and Prevention (U.S. CDC) and the World Health Organization (WHO). Specific factors need specific consideration in the management of PID; these include the presence of human immunodeficiency virus infection, use of intrauterine devices (IUDs), incarceration, and sexual violence.

Definition

PID is generally a sexually transmitted disease characterized by upper genital tract infection in females (1) (*Figure 1*). It is often initiated by the presence of *Neisseria gonorrhoeae* (*N. gonorrhoeae*) and/or *Chlamydia trachomatis* (*C. trachomatis*) in the lower genital tract that ascend to infect the uterus, fallopian tubes and ovaries. PID often becomes a polymicrobial infection due to the presence of various vaginal-cervical endogenous microbes (1,2).

Epidemiology

There are approximately one million PID cases that are identified each year in the U.S. and approximately one-third are diagnosed in adolescent females. After a steady decline in initial office visit for PID until 2014, a rising trend is recently reported (*Figure 2*). Finding precise PID epidemiologic figures can be challenging due to differences in surveillance in various regions as well as countries, natural variation in PID prevalence, and difficulty of distinguishing cervicitis from overt PID (1,3,4).

Pathophysiology

Classic PID is an infection that begins in the cervical-vaginal region and ascends to the upper genital tract

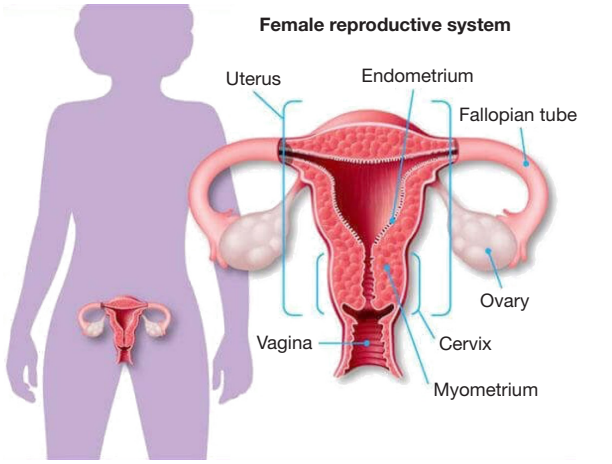

Figure 1 Female reproductive system. Source: https://www.womenshealth.gov/files/images/female-reproductive-system.jpg accessed 5/31/2019. A federal government website managed by the Office on Women's Health in the Office of the Assistant Secretary for Health at the U.S. Department of Health and Human Services.

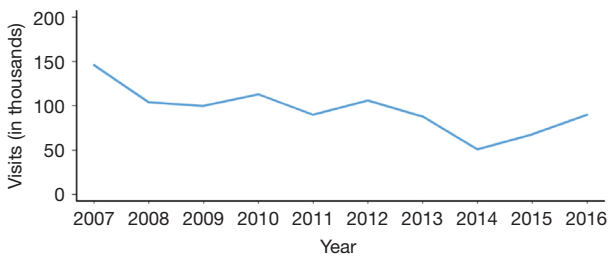

Figure 2 Pelvic inflammatory disease—initial visits to physicians' offices among women aged 15–44 years, United States, 2007–2016. Source: National Disease and Therapeutic Index, IMS Health, Integrated Promotional Services™, IMS Health Report, 1966–2016. Content source: Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention (https://www.cdc.gov/std/stats17/figures/a.htm, accessed 5/31/2019). STD, sexually transmitted disease; TB, tuberculosis.

resulting in a combination of features; these include acute salpingitis, perihepatitis, endometritis, oophoritis, pelvic peritonitis and/or tubo-ovarian abscess (TOA) (1,2,5). Scarring, adhesions and obstruction of the fallopian tubes may result from PID-induced inflammation. Loss of the ciliary epithelial cells of the fallopian tube impairs ovum transport and augments the risk for infertility as well as ectopic pregnancy; chronic pelvic pain may develop due to adhesions (6).

Table 1 Microbes associated with in pelvic inflammatory disease

Chlamydia trachomatis
Neisseria gonorrhoeae
Gardnerella vaginalis
Haemophilus influenzae
Bacteroides species (*B. fragilis*, *bivius*, *disiens*)
Mycoplasma genitalium
Group B streptococcus (*S. agalactiae*)
Coliforms (*Enterobacteriaceae*)
Peptostreptococcus
Streptococcus faecalis
Ureaplasma urealyticum
Neisseria meningitides
Mycoplasma hominis
Enterococcus
Cytomegalovirus
Other *anaerobes*

Studies reveal that *C. trachomatis*-induced PID is more frequent in the 16- to 24-year old female [versus *Neisseria gonorrhoeae* (*N. gonorrhoeae*) initiation] (3). Microbiology findings of PID research show that *C. trachomatis* is found in up to 43% (10–43%) of PID cases and *N. gonorrhoeae* is noted in up to 50% (25–50%). Other microbes are seen in 30% of PID cases; these include enteric and respiratory microbes, cervical pathogens (i.e., *Mycoplasma genitalium*), bacterial vaginosis agents, and other bacteria (i.e., anaerobic and facultative) (*Table 1*).

Risk factors

Research has identified a number of risk factors in PID development that include young age (i.e., adolescence or young adulthood), ectropion of young adolescent females, immature immune system, multiple coital partners, ineffective condom usage, past PID, presence of bacterial vaginosis, vaginal douching, coitus during menstruation, and history of non-barrier contraception (1).

The highest PID prevalence is found in adolescent females 15 to 19 years of age who initiate their coital experience early in adolescence (*Figure 3*), have multiple

Table 2 Factors associated with *C. trachomatis*-induced fallopian tube damage

Stimulation of the innate immune receptor with Toll-like receptor 1
Anti-C trachomatis antibodies (i.e., 60-kDa heat shock protein 60)
$CD4^+$ T cell responses
Immune responses of TH1
Immune responses of TH17

C. trachomatis, *Chlamydia trachomatis*.

coital partners, and fail to utilize effective contraception or contraceptive methods in a recommenced manner (1,7). An additional risk factor for young adolescent females is the presence of immature cervix that contains columnar epithelium transitional zone that can be a positive milieu for *N. gonorrhoeae* and *C. trachomatis*.

Trauma to the endocervical canal from an IUD may facilitate the ascent of microorganisms into the endometrial cavity. Multifilament IUD tails strings were implicated earlier with increased risk for infection; however, current research reveals that PID risks do not rise with insertion of monofilament tail string IUDs (1,8). Even so, expert recommendations for the placement of IUDs in adolescent females usually state that *C. trachomatis* and *N. gonorrhoeae* screening occur when inserting the IUD (9,10).

Complicating the PID in the adolescent females is their immature immune system; this includes the immaturity of antibody and $CD4^+$ T cell responses that fail to eliminate *C. trachomatis* and the resultant potential for a silent infection (11). Chronic fallopian tube damage can result from chronic inflammation due to various factors that include cell-autonomous immunity and the effects of interstitial or stromal cells (i.e., telocytes) (*Table 2*) (1,12-14).

Not only can repeated *C. trachomatis* infection lead to fallopian tube damage, but tubal injury may occur from *N. gonorrhoeae* via release of lytic transglycosylases (LTg) (1). LTgA and LTgD can induce the development and release of peptidoglycans that can damage fallopian tube cells (15,16).

Specific considerations

Sexual violence

Individuals may be hesitant to get medical care if they have been victims of sexual violence including rape (17). Medical practitioners should understand that these adolescents and young adults may be reluctant to seek timely medical care if there is a history of sexual violence. Psychological support is needed by caring and understanding health care professionals to provide beneficial support in such potentially difficult circumstances.

Incarceration

Adolescents in jail or jail-like facilities have an increased incidence of *C. trachomatis*, *N. gonorrhoeae*, PID and other sexually transmitted infections (STIs) (1). Thus, it is important to provide robust STI screening programs to these youths with appropriate treatment as well (18).

Lesbian, bisexual, and transgender youth

Other youth who may be reluctant to seek healthcare for their sexuality issues include those who identify as lesbian, bisexual and transgender; also, medical practitioners may assume that some of these persons are not at risk for PID (19,20). Thus, medical practitioners caring for all youth must be vigilant for the health care needs of all their young patients and obtain a careful as well as detailed history on their medical needs (21).

HIV

Females diagnosed with PID should be screened for other STIs including HIV and also for being victims of sexual violence (22,23). Management of females with PID in women with HIV is similar to those without associated HIV; however, some data suggests that this combination of disorders may induce an increase in concomitant infection with certain microbes (i.e., *streptococci*, *Mycoplasma hominis*) as well as increased risk for TOA (24).

Clinical features

A wide variety of symptoms can be seen in females with PID and thus, accurate diagnosis can be clinically challenging (1). Patients may exhibit few or no symptoms, whereas others have acute, serious illness. The most common presenting complaint is lower abdominal pain. Gonorrheal PID is the most severe form whereas chlamydial PID is more likely to be subclinical with little or no symptoms, but with potentially adverse long-term consequences (6). In a sample of endometrial biopsies, 13% females with PID were diagnosed with subclinical PID (25,26). Although sparse

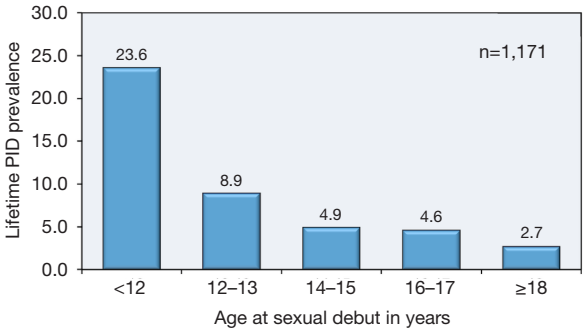

Figure 3 Prevalence of self-reported lifetime PID and age of sexual debut. In NHANES 2013–2014, 1,171 sexually experienced women 18–44 years of age were interviewed regarding a lifetime diagnosis of PID. This graph shows the correlation of age of sexual debut and lifetime prevalence of PID. Source: US Centers for Disease Control and Prevention: Kreisel K, Torrone E, Bernstein K, *et al.* Prevalence of Pelvic Inflammatory Disease in Sexually Experienced Women of Reproductive Age - United States, 2013-2014. MMWR Morb Mortal Wkly Rep 2017;66:80-3. PID, pelvic inflammatory disease; NHANES, National Health and Nutrition Examination Survey.

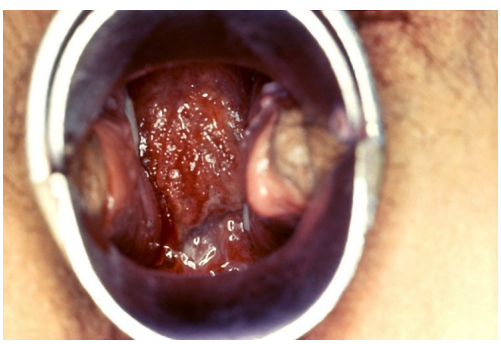

Figure 4 Chlamydia trachomatis infection. This image depicts a colposcopic view of a female patient's cervix, which had manifested signs of erosion and erythema, due to a *Chlamydia trachomatis* infection. If left untreated, chlamydia infection can cause severe, costly reproductive, and other health problems. Both short- and long-term consequences can ensue, including pelvic inflammatory disease (PID), infertility, and potentially fatal, ectopic tubal pregnancies.

symptoms may be seen in PID, its classic presentation is vaginal (cervical) discharge (*Figure 4*) and lower abdominal (lower quadrant; pelvic) pain (1).

Other features of PID include vaginal bleeding, urinary symptoms (i.e., dysuria, urinary frequency), post-coital bleeding and/or dyspareunia (1-3,5). Others include fever, chills, and protean gastrointestinal symptoms (i.e., nausea, emesis, constipation, and diarrhea). The condition can also manifest with an acute abdominal crisis with rebound tenderness and reduced bowel sounds. A pelvic examination may reveal cervical motion tenderness and there may or may not be uterine or adnexal tenderness (1-3,5).

Studies reveal that about 4% (3–10%) of those with PID also have Fitz-Hugh-Curtis syndrome (perihepatitis) due to the spread of the lower genital tract inflammation/infection in the paracolic gutter that induces inflammation of the liver's Glisson's capsule and local peritoneum (1). Perihepatitis symptomatology includes fever, nausea, emesis, abdominal pain (right upper quadrant pain), right pleural effusion and/or right shoulder pain (1,27-31). In such cases there is typically right upper quadrant tenderness but no lower abdominal pain. Medical practitioners should consider perihepatitis (Fitz-Hugh-Curtis syndrome) in sexually active females who have right upper quadrant pain (32). Severe infection with *N. gonorrhoeae* may progress to disseminated gonococcal infection (*Figure 5*).

Diagnosis

Diagnostic criteria for PID from the U.S. CDC are listed in *Table 3* that include minimal criteria, additional criteria and specific criteria (24) (*Figure 6*). All females suspected of PID should be tested for *N. gonorrhoeae* and *C. trachomatis* infection using nucleic acid amplification tests. Although the diagnosis of PID in most cases is based on clinical findings, when indicated, it can be aided by the following: laparoscopy (81% sensitivity versus 100% specificity), magnetic resonance imaging, transvaginal sonography (30% sensitivity versus 67% specificity), and endometrial biopsy (74% sensitivity versus 84% specificity) (1,24,32).

The diagnosis of PID in emergency rooms and clinics is often based on clinical criteria, with or without additional laboratory and imaging tests (33). Clinical findings have a sensitivity of 87% and a specificity of 50% versus 83% sensitivity and 26% specificity of endometrial culture (1,2,24,32).

Table 4 lists the differential diagnosis of PID and reveals the clinical challenge that can arise in a sexually active female with PID-like symptoms. Many possibilities must be considered including genitourologic, gynecologic, gastrointestinal, rheumatologic, hematologic and others (1,24,32). A pregnancy test should be performed to exclude the possibility of ectopic pregnancy. An augmented level of

Table 3 U.S. CDC 2015 Diagnostic criteria for pelvic inflammatory disease (24)

Category of criteria	Specific criteria data
Minimal criteria (≥1)	Cervical motion tenderness, or uterine tenderness, or adnexal tenderness
Additional criteria (≥1 to support minimal criteria for PID)	Oral temperature over 101 °F (over 38.3 ℃)
	Abnormal cervical mucopurulent discharge or cervical friability
	Presence of abundant numbers of WBC on saline microscopy of vaginal fluid
	Elevated erythrocyte sedimentation rate
	Elevated C-reactive protein; and
	Laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*
Most specific criteria	Endometrial biopsy with histopathological evidence of endometritis
	Findings of PID on laparoscopy
	Ultrasound (transvaginal) or magnetic resonance imaging showing fallopian tubes that are thick and filled with fluid; may be free fluid in the pelvis or a tubo-ovarian complex; or
	Doppler studies suggestive of pelvic infection via tubal hyperemia

U.S. CDC, United States Centers for Disease Control and Prevention; PID, pelvic inflammatory disease.

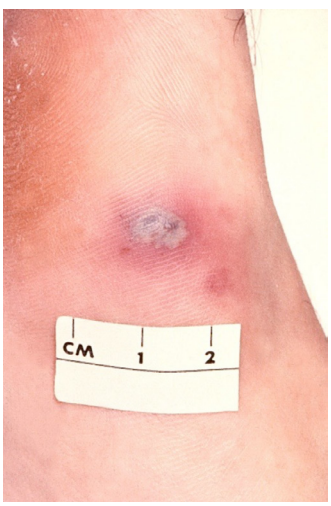

Figure 5 Cutaneous gonococcal lesion. This patient presented with a cutaneous gonococcal lesion due to a disseminated *Neisseria gonorrhoeae* bacterial infection. Though a sexually transmitted disease, if a *gonorrhoeae* infection is allowed to go untreated, the *Neisseria gonorrhoeae* bacteria responsible for the infection can become disseminated throughout the body, forming lesions in extra-genital locations (https://phil.cdc.gov/Details.aspx?pid=6384, accessed 5/31/2019).

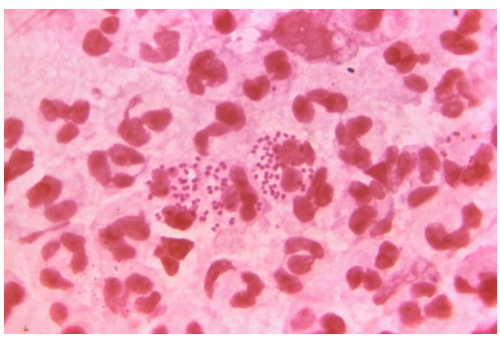

Figure 6 Gram stain positive for *N gonorrhoeae*. This Gram-stained photomicrograph reveals the presence of intracellular Gram-negative, *Neisseria gonorrhoeae* diplococcal bacteria, amongst numerous white blood cells (WBCs) known as polymorphonuclear leukocytes, or PMNs (https://phil.cdc.gov/Details.aspx?pid=15018, accessed 5/31/2019).

serum procalcitonin can be a marker for TOA (34). Medical practitioners must also consider that PID can develop in non-sexually active females in uncommon cases (35-38).

In virginal adolescents, PID may originate from the lower genital tract, urinary tract, gastrointestinal tract and may be associated with genital or other anomalies (39).

Treatment

Treatment of PID involves an early diagnosis along with the recognized protocols such as the 2001 WHO (40) (*Table 5*) or the 2015 CDC sexually transmitted diseases

Table 4 Differential diagnosis of pelvic inflammatory disease

Acute intermittent porphyria
Adnexal torsion
Appendicitis
Constipation
Cystitis (urinary tract infection)
Diverticulitis
Dysmenorrhea
Endometriosis
Ectopic pregnancy
Fallopian tube torsion
Functional abdominal pain
Gastroenteritis (as due to *Yersinia enterocolitica* or *Campylobacter fetus*)
Genital trauma
Henoch-Schonlein syndrome
Hemolytic-uremic syndrome
Inflammatory bowel disease
Irritable bowel disease
Lead intoxication
Lupus serositis
Meckel's diverticulum
Mesenteric lymphadenitis
Mesenteric vascular disease
Ovarian cyst (with or without torsion or rupture)
Ovarian neoplasm (including teratoma rupture)
Ovulation (Mittelschmerz)
Pelvic adhesions
Pregnancy complication
Pyelonephritis
Reiter's syndrome
Septic abortion
Sickle cell crisis
Urethritis
Ureterocele
Urolithiasis

guidelines (*Table 6*) (24). Such antibiotic courses cover various microbes seen in PID such as *C. trachomatis*, *N. gonorrhoeae*, *Mycoplasma genitalium*, and various facultative/anaerobic bacteria (1,24). Use of these recommended antibiotics should lead to observable symptomatology improvement in two to three days that includes no fever, reduction in abdominal pain (tenderness, rebound), and reduced pelvic pain (less cervico-utero-adnexal motion tenderness). *Table 7* lists indications for hospitalization.

Intravenous antibiotics can be converted to oral administration after 24 hours of improvement. The use of metronidazole can also treat bacterial vaginosis that may also be present (1). Oral use of doxycycline is preferred since intravenous administration of this antibiotic can be quite painful (1).

A variety of problems arise in treatment including increasing bacterial resistance to antibiotics, i.e., quinolone-resistant *N. gonorrhoeae* (*QRNG*) and reduced efficacy of third-generation cephalosporins (1,41). Therefore, quinolones are no longer recommended for the treatment of *gonorrhoeae* (41,42). The ease of travel across regions and countries has led to continuous changes in other bacteria as well—such as the prevalence and antibiotic resistances of *Mycoplasma genitalium*, *Ureaplasma urealyticum* and others (43-45). Complicating this picture is the failure of some medical practitioners to follow established guidelines (46-49).

Careful management of PID is important to reduce discomfort, improve symptoms as soon as possible, and potentially reduce the complications that include chronic pelvic pain, ectopic pregnancy and infertility (1,26,50). In the classic research of Weström *et al.* dealing with a large cohort of women, laparoscopic evaluations revealed a PID-associated infertility rate of 16% (versus 2.7% in controls); also, 9.1% of post-PID pregnancy were ectopic pregnancies (versus 1.4% of controls) (50).

According to the WHO (51) and CDC (52) Medical Eligibility Criteria for Contraceptive Use, there is insufficient evidence to recommend removal of the IUD in the case of acute PID. However, close clinical follow-up is recommended if the IUD is left in place (53). Patients with PID should be tested for other STIs (including HIV). Sexual partner/s should be evaluated and treated when indicated. The U.S. CDC recommends treatment of the PID patient's sexual partner (s) over the past 2 months even

Table 5 Antibiotic management of PID (2001 WHO Model Prescribing Information: Drugs used in Bacterial Infections) (40)

Type of patient	Recommended antibiotics
Ambulatory patients	Ceftriaxone 250 mg IM in a single dose followed by doxycycline 100 mg orally every 12 hours for 10 days (contraindicated during pregnancy), plus metronidazole 400–500 mg orally every 8 hours for 10 days (contraindicated during pregnancy)
Hospitalized patients with moderate or severe disease	Ceftriaxone 25 mg IM every 12 hours for at least 4 days (or for 48 hours after clinical improvement occurs), followed by doxycycline 100 mg orally every 12 hours for 10–14 days (contraindicated during pregnancy)
Hospitalized patients with very severe disease	Gentamicin 5–7 mg/kg IV or IM every 24 hours or 1.5–2.0 mg/kg IV or IM every 8 hours for at least 4 days (or for 48 hours after clinical improvement occurs; contraindicated during pregnancy; plus clindamycin 900 mg IV every 8 hours for at least 4 days (for 48 hours after clinical improvement occurs) followed by doxycycline 100 mg orally every 12 hours for 10–14 days (contraindicated during pregnancy)

PID, pelvic inflammatory disease; IM, intramuscular; IV, intravenous.

Table 6 Antibiotic management of PID: U.S. CDC 2015 STI guidelines

Method of delivery	Recommended antibiotics
Oral/intramuscular	Ceftriaxone 250 mg IM in a single dose or cefoxitin 2 g IM in a single dose and probenecid 1 g orally concurrently or other parenteral third generation cephalosporin (as ceftizoxime or cefotaxime); plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days
Parenteral	Regimen A: cefotetan 2 g IV every 12 hours or cefoxitin 2 g IV every 6 hours plus doxycycline 100 mg orally or IV every 12 hours
	Regimen B: clindamycin 900 mg IV every 8 hours plus gentamicin loading dose IV or IM (2 mg/kg body weight) followed by a maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing (3–5 mg/kg) can be substituted
	Alternative: ampicillin/Sulbactam 3 g IV every 6 hours plus doxycycline 100 mg orally or IV every 12 hours

U.S. CDC, United States Centers for Disease Control and Prevention; STI, sexually transmitted infection; PID, pelvic inflammatory disease; IM, intramuscular; IV, intravenous.

Table 7 Considerations for hospital-based treatment for PID

High fever
Intractable nausea or vomiting (including loss of medications due to vomiting)
Inability to follow outpatient protocols
Pregnancy
Possibility of appendicitis or other surgical emergency
Tubo-ovarian abscess
Failure of oral antimicrobial therapy

PID, pelvic inflammatory disease.

though they may be asymptomatic; principles of expedited partner therapy (EPT) are suggested (1,24). The treated PID patient should be seen in 3 to 6 months post-treatment and provided with further sexuality education (1,24).

Prevention

Various STI/PID screening programs have been utilized around the world over the past few decades such as that of the annual *C. trachomatis* screening recommended by the U.S. Preventive Service Task Force (USPSTF) for all sexually active females under age 26 years of age (54). Medical practitioners can also recommend screening utilizing the "self-taken swab" that is done by the person being screened in which the examination of the swab can detect both *C. trachomatis* and *N. gonorrhoeae* with nucleic acid amplification technology (55,56). One study noted a 56% lowering of PID incidence in sexually active females (18 to 34 years of age) who received appropriate *C. trachomatis* screening (57). Limitations to such success of screening programs may occur if the screening is limited, medical practitioners are not motivated to provide/encourage such policies, or public health officials in various countries view

Table 8 Strategies for prevention of pelvic inflammatory disease

Education to delay adolescent coital activity
Education about correct condom use
Education of potential cause of abdominal pain and need for medical evaluation in such situations
Comprehensive sexuality education in schools
Include sexuality education to those at high-risk for STIs—runaway teens, incarcerated teens
Further research on immunological defenses for infections
Further research on vaccines for STIs (as *C. trachomatis* and *N. gonorrhoeae*)

STI, sexually transmitted infection; *C. trachomatis*, *Chlamydia trachomatis*; *N. gonorrhoeae*, *Neisseria gonorrhoeae*.

such programs as too costly (58-60). *Table 8* lists other prevention considerations that have been utilized to reduce PID as well as other STIs.

Conclusions

PID is a common sexually transmitted disease found among sexually active adolescents and young adults as well as older adult females (1). Those with PID may present with vaginal-cervical discharge, lower abdominal pain, cervical motion tenderness and bilateral adnexal tenderness. A variety of symptomatology may occur including a paucity of symptoms. The differential diagnosis is considerable and a careful evaluation is needed to identify the correct diagnosis. PID requires antibiotics as per established protocols such as found with the CDC and the WHO. Careful follow-up is needed to reduce potential PID complications. Each country should establish comprehensive sexuality education that includes STI prevention education (1,61).

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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