Clinical Review

Pelvic Inflammatory Disease

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The rising incidence of pelvic inflammatory disease (PID), coupled with the development of more sophisticated and effective diagnostic techniques, has created a new body of knowledge regarding the microbiology, diagnosis, and natural history of this disease. Acute pelvic inflammatory disease is the major gynecologic health problem in the United States. Distinguishing acute PID from the other causes of acute pelvic pain is often a difficult task. Careful consideration of a patient's risk profile for PID and utilization of the diagnostic techniques available are invaluable in helping the clinician accurately make this differentiation. The microbial spectrum involved in PID is complex and must be taken into consideration when selecting an antibiotic regimen. The recent addition of new, broad-spectrum antibiotics to the physician's therapeutic armamentarium has led to increasingly effective management options. Despite the effectiveness of current medical and surgical therapy, the staggering economic, medical, and social consequences of PID mandates more aggressive efforts at its prevention.

The United States has been in the midst of a venereal disease epidemic since the mid-1960s.[1] Coincident with this epidemic has been a rising incidence of pelvic inflammatory disease (PID), which is associated with major medical and economic consequences. It is one of the leading causes of infertility in the world[2] and is primarily responsible for the recent tripling of ectopic pregnancies in the United States.[3] Pelvic inflammatory disease also accounts for 5 to 20 percent of gynecologic hospital admissions in the United States[4] and 2.5 million outpatient physician visits annually. It has been estimated that direct and indirect costs of PID exceeded $1.25 billion in 1979.[1]

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Incidence

Pelvic inflammatory disease is not a reportable disease, and accurate incidence rates are not available. Estimates of its incidence are hampered by the incomplete reporting of gonorrhea cases throughout the United States. Estimated annual

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incidence in the United States ranges from 500,000 to 2 million cases.

Epidemiology

Numerous epidemiological factors have been associated with PID. These factors have important implications, not only in assessing a patient's risk of having PID, but also in counseling women with respect to contraception.

Age

The highest incidence of PID occurs in sexually active females less than 25 years old.[5,6] The female adolescent is felt to be a very high risk, and it has been estimated that one out of eight sexually active adolescent girls will develop acute PID.[7]

Parity

The data regarding parity are somewhat conflicting, with some authors feeling that nulliparous women are at an increased risk for PID and others seeing no relationship between gravidity and risk.[8]

Race

Nonwhite groups are generally regarded as being at an increased risk for PID.[9]

Socioeconomic Status

Pelvic inflammatory disease is felt to be more common in the indigent population.[5]

History of Pelvic Inflammatory Disease

The woman who has had a prior episode of PID is at a higher risk for a subsequent one. Once a patient has had PID, her risk of having another episode is increased two to three times.[5] Westrom found a 23 percent recurrence rate when following 415 women with acute PID.[6]

Marital Status

St. John et al[10] found that the risk of being hospitalized with PID was three to four times higher among divorced and separated women than among married women.

Number of Sexual Partners

It has been estimated that having multiple sex partners raises a woman's chances of developing PID by 3[5] to 4.6 times.[9]

Method of Contraception

A woman's method of contraception strongly influences her risk profile for the development of PID. The intrauterine contraceptive device has been clearly established as a risk factor for PID,[11] increasing a woman's relative risk two to nine times.[12] It has been estimated that 0.6 to 3.5 percent of intrauterine device users will develop PID[9] and that 22 percent of cases of PID are attributable to the intrauterine device.[13] On the other hand, barrier methods of contraception (condom, diaphragm, spermicidal jelly) are felt to be protective against PID.[9] Although somewhat controversial, it is now generally felt that oral contraceptive users are at a decreased risk for developing PID.[8,14]

Pathogenesis

Pelvic inflammatory disease has been classically categorized into "gonococcal PID" and "nongonococcal PID" on the basis of endocervical cultures for Neisseria gonorrhoeae. Acute PID is a complex disorder in which organisms in the lower genital tract (endocervix, vagina) ascend for unclear reasons into the upper genital tract. The resulting infection then contiguously spreads, producing inflammation of the endometrium (endometritis), fallopian tubes (salpingitis), ovaries (oophoritis, tubo-ovarian abscess), and adjacent structures such as the parametrium (parametritis) and the peritoneal cavity (peritonitis, pelvic abscess).[15]

During the past decade, advances in microbiological culture techniques (anaerobic cultures, tissue cultures), new serological testing, and the increased utilization of culdocentesis and laparoscopy to obtain culture specimens have unfolded a complex polymicrobial spectrum for PID.[14] The four groups of organisms most commonly implicated are N gonorrhoeae, Chlamydia trachomatis, nongonococcal aerobic and anaerobic bacteria, and the genital mycoplasmas.[5]

Although these organisms have been linked to PID, their exact roles in the pathogenesis of PID is not so clearly defined. The term "primary patho-

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gen'' refers to organisms that are able to initiate infection de novo and damage a ''normal'' upper female genital tract. N gonorrhoeae is definitely felt to be a primary pathogen,[16] and most investigators also place C trachomatis in this category.[17] The term ''secondary pathogen'' refers to opportunistic organisms that are not normally pathogenic but acquire this potential when introduced into a system that is immunologically compromised. This compromised state can arise by a number of postulated mechanisms, including (1) damage to the upper female genital tract inflicted by a prior infection (initiated by a primary pathogen) resulting in a diminution of local microbiological defense mechanisms,[5] (2) the presence of an intrauterine device disrupting the normal protective barrier of the uterus by allowing vaginal organisms to pass into the uterus along its transcervical trail,[18] and (3) the presence of a nonspecific vaginitis possibly related to sexual activity or produced by an intrauterine device.[5]

Symptoms and Signs

The most common complaint of patients with PID is lower abdominal pain, and many investigators have required that it be present for the diagnosis of PID to be even considered[2,7]; nevertheless, it may be absent in up to 6 percent of the cases.[19] The pain is generally of less than 15 days duration and is exacerbated by movement, sexual intercourse, and performance of a Valsalva maneuver.[10] Other common symptoms include vaginal discharge in 55 to 57 percent of cases, abnormal vaginal bleeding in 30 to 40 percent, dysuria in 19 to 37 percent, and gastrointestinal complaints (nausea, vomiting, anorexia) in 25 percent.[19]

The most common signs elicited on physical examination are abdominal and adnexal tenderness, present in nearly all cases. The adnexal tenderness may be unilateral in 6 to 8 percent of the cases.[10] Right upper quadrant abdominal tenderness consistent with the Fitz-Hugh-Curtis syndrome (perihepatitis) is present in 1 to 31 percent of cases of gonococcal PID,[12] and there is evidence to suggest that C trachomatis can produce perihepatitis as well.[20] Other common findings on examination include cervical motion tenderness in 97 percent of cases,[5] adnexal enlargement in 25 to 49 percent, abnormal vaginal discharge in 32 to 63 percent, and fever in as few as 33 to 35 percent.[5,19]

Differential Diagnosis

Distinguishing PID from the other causes of acute pelvic pain is frequently a difficult task. Jacobson and Westrom[19] were able to confirm the diagnosis of PID laparoscopically in only 65 percent of 814 women suspected clinically of having PID. Twelve percent of their cases diagnosed clinically as PID were found to have other intra-abdominal or intrapelvic disorders, and 23 percent had no visual pathologic changes at all. Conditions that can be mistaken for PID include ectopic pregnancy, appendicitis, torsion or rupture of an ovarian cyst, endometriosis, corpus luteal cyst bleeding, hemorrhagic follicular cyst, septic abortion, ovarian tumor, urinary tract infection, and pelvic adhesions.[12,19]

In view of the clinical diagnosis of acute PID being frequently inaccurate, corroborative data should be routinely sought to avoid misdiagnosing other potentially serious intrapelvic and intra-abdominal disorders as PID.

Laboratory Aids

White Blood Count

The white blood cell count is neither sensitive nor specific for diagnosing PID. It is elevated in numerous inflammatory conditions other than PID. Additionally, leukocytosis may be absent in 44 to 53 percent of cases of PID.[5,12]

Erythrocyte Sedimentation Rate

The erythrocyte sedimentation rate is also a nonspecific screening test for inflammation, although it is generally elevated in acute PID. Nevertheless, Jacobson and Westrom found it to be normal (less than 15 mm/h) in 24 percent of women with laparoscopically documented PID.[19]

Cervical Gram Stain

Gram stain of the cervical exudate is a poor screening procedure for gonorrhea in asymptomatic women because of its low sensitivity and specificity.[21] However, some investigators feel that it can be useful in evaluating women with suspected PID.[5,15] Eschenbach et al,[22] using ''gram-negative diplococci seen within three or more neu-

trophils" as the criteria for a positive Gram stain for gonorrhea, found it to be a valuable diagnostic tool with a sensitivity of 67 percent and a specificity of 98 percent.

Cervical Cultures

Cervical cultures for gonorrhea, although not providing immediate data, are recommended to distinguish gonococcal PID from nongonococcal PID.[23] This distinction is therapeutically and prognostically important, since nongonococcal PID is more likely to be associated with a polymicrobial infection,[5] to have a slower clinical response to antibiotic therapy,[24] to result in the formation of a pelvic abscess,[24] and to cause infertility.[6] Culturing for nongonococcal bacteria is not felt to be useful, since the cervical flora is not an accurate reflection of the microbial milieu infecting the upper genital tract.

Examination of Male Sex Partner(s)

The diagnosis of urethritis in a patient's male sex partner(s) supports the diagnosis of acute PID. Since a substantial number of men with gonococcal and nongonococcal urethritis are asymptomatic,[5] a Gram stain and culture is indicated even if the male partner denies symptoms. The presence of gram-negative intracellular diplococci on urethral Gram stain is consistent with the diagnosis of gonococcal urethritis. Five or more polymorphonuclear leukocytes per field in five high-power fields (×1000) without gram-negative intracellular diplococci is consistent with nongonococcal urethritis.

Pregnancy Testing

Recent advances in pregnancy testing include the radioreceptor assay (RRA) for human chorionic gonadotropin (hCG) and the radioimmunoassay for the β-subunit of hCG. The RRA (Biocept-G, Wampole Laboratories, Cranbury, NJ) has a sensitivity of 200 mIU/mL and is positive in 94 percent of cases of ectopic pregnancy.[25] The radioimmunoassay has a sensitivity of 5 mIU/mL and a 100 percent sensitivity for ectopic pregnancy[26]; thus, a negative result effectively excludes the diagnosis. Both of these tests are useful in assessing a patient's risk for ectopic pregnancy and are thereby invaluable in the diagnostic evaluation of the woman presenting with acute pelvic pain. In view of the not infrequent difficulty encountered in distinguishing ectopic pregnancy from PID in women with acute pelvic pain and the potentially diastrous consequences that may stem from this, the clinician should have a low threshold for the invocation of these tests.

Adjunctive Diagnostic Studies

Culdocentesis

Culdocentesis is a rapid, safe, valuable procedure in the evaluation of acute pelvic pain. Hemoperitoneum, diagnosed when nonclotting blood is aspirated from the cul de sac, is present in 82 percent of ectopic pregnancies. Berry et al[25] found that the combination of culdocentesis and the Biocept-G radioreceptor assay detected 97 percent of ectopic pregnancies. If clear serous fluid is obtained, the diagnosis of a ruptured ovarian cyst is supported.[27] The diagnosis of PID is substantiated if purulent fluid is obtained, although other causes of peritonitis (ruptured appendix, ruptured diverticular abscess) can produce a similar finding.

In view of the estimate that 30 percent of bacterial isolates obtained via culdocentesis represent vaginal contaminants, Cunningham et al[28] proposed that the Gram stain of the peritoneal fluid be used to differentiate pathogens from contaminants. Culdocentesis is most likely to be productive in patients with moderate to severe PID,[5] although some authorities advocate its routine usage in all cases of suspected salpingitis.[27] Contraindications to culdocentesis are the presence of a mass in the cul de sac (absolute) and a markedly retroflexed uterus (relative).[29]

Pelvic Ultrasound

The value of pelvic ultrasound in the initial evaluation of patients with acute pelvic pain has been recently demonstrated.[30] Ultrasound findings consistent with PID include increased visibility of the fallopian tubes with associated fluid-containing areas, enlargement of the ovaries, tubes, and ligaments, and the presence of a complex, multiloculated mass with cystic and solid elements incorporating the uterus (tubo-ovarian abscess). In the appropriate clinical setting the diagnosis of acute

PID is easily confirmed by ultrasonography. It should be noted, however, that in the majority of cases, sonographic findings of PID are indistinguishable from those of other intraperitoneal disorders (ectopic pregnancy, endometriosis, ovarian cysts, etc), and careful clinical correlation is required.[31] Pelvic ultrasound has been found to be a highly accurate (95 percent) method of diagnosing pelvic abscesses[32] and can be utilized to monitor their response to medical therapy.

Laparoscopy

An important role for laparoscopy in the diagnosis of acute pelvic pain has been well established, and its employment often negates the need for exploratory laparotomy.[19] Laparoscopic findings consistent with PID include purulent exudate from the fimbriated end or serosal surface of the fallopian tube, erythema of the fallopian tube, edema and swelling of the fallopian tube, or an inflammatory mass, such as a pyosalpinx or tuboovarian abscess, involving the fallopian tube. In addition to its diagnostic capabilities, laparoscopy is also felt to provide material for culture that most accurately reflects the microbiology involved in the pathogenesis of acute PID.

Although it has been recommended that diagnostic laparoscopy be used routinely in all cases of suspected PID,[19] the risk-benefit ratio of such an approach has not been clearly established. Nevertheless, diagnostic laparoscopy is clearly indicated in the patient with acute pelvic pain in whom the diagnosis of PID is not clear and in whom other potential life-threatening disorders (ectopic pregnancy, appendicitis, etc) needs to be excluded.[33] Additionally, laparoscopy should be strongly considered in cases of PID unresponsive to antibiotic therapy.

Management

Criteria for Hospital Admission

After the diagnosis of PID is established, the first decision to be made by the clinician is whether the patient requires hospitalization. Numerous clinical criteria meriting hospital admission have been proposed,[12,23] including an uncertain diagnosis in which surgical emergencies such as appendicitis and ectopic pregnancy must be excluded, presence of an adnexal mass or suspected pelvic abscess, pregnancy, evidence of generalized peritonitis, inability of a patient to follow or tolerate an oral outpatient antibiotic regimen, failure to respond to outpatient management, or temperature greater than 38.4°C.

Antibiotic Therapy

Antibiotics remain the cornerstone of therapy for acute PID. Although the polymicrobial nature of PID has been well established, many of the current treatment regimens are based on the premise that N gonorrhoeae is the major etiologic agent involved in PID. In selecting an antibiotic regimen, the clinician must be aware of the therapeutic limitations of each of the regimens and of the clinical situations in which a broader antimicrobial coverage is likely to be required.

Approximately two thirds to three fourths of patients with acute PID are treated on an outpatient basis.[4,7] Since it is difficult to distinguish gonococcal PID from nongonococcal PID, most clinicians simply utilize the recommended treatment schedule proposed by the Centers for Disease Control intended for gonococcal PID.[23] These recommendations are as follows: tetracycline, 0.5 g orally, four times a day for 10 days in nonpregnant patients; or aqueous procaine penicillin G, 4.8 million units intramuscularly; ampicillin, 3.5 g orally; or amoxicillin, 3 g orally—each with 1.0 g of probenecid. Either regimen is followed by ampicillin, 0.5 g orally, or amoxicillin, 0.5 g orally, four times a day for 10 days. Although only the tetracycline schedule would be expected to be effective against C trachomatis, Cunningham et al found an 82 percent clinical cure rate in 197 patients with PID (63 percent with gonococcal PID) with no significant difference between the two regimens.[24]

A role for doxycycline, an analogue of tetracycline, in the outpatient therapy of acute PID has been advocated.[34] Doxycycline provides adequate coverage against both gonorrhea and Chlamydia, is considerably more active in vitro than tetracycline against a variety of other aerobic and anaerobic bacteria, achieves effective antibiotic concentrations throughout the uppper female genital tract, and has a long half life, allowing a more convenient dosing regimen (which enhances patient compliance).[35] The usual dosage employed is

a loading dose of 200 mg followed by 100 mg daily or twice daily for 10 days.

Patients hospitalized for acute PID can be started on one of numerous parenteral antibiotic regimens. Single drug therapy is most likely to be effective in PID uncomplicated by peritonitis (documented on culdocentesis), tubo-ovarian abscess, pelvic abscess, or pyosalpinx.[2] Commonly used single drug regimens include the following:

1. Aqueous crystalline penicillin G, 20 million units given intravenously each day until improvement occurs, followed by ampicillin 0.5 g orally four times a day to complete 10 days of therapy.[23]
2. Tetracycline, 0.25 g intravenously every six hours until improvement occurs, followed by 0.5 g orally four times a day to complete 10 days of therapy.[23]
3. Ampicillin, 2 g intravenously every six hours until improvement occurs, followed by 0.5 g orally every six hours to complete 10 days of therapy.
4. Doxycycline, 200 mg intravenously over 30 minutes, followed by 100 mg intravenously every 12 hours until improvement occurs, then 100 mg orally every 12 hours to complete 10 days of treatment.[2]

For patients who fail to respond to the single drug regimens listed as well as for patients with severe PID (peritonitis, inflammatory masses, etc), broader antimicrobial coverage should be provided.[2,4,12] The antibiotic regimen chosen should be effective against not only the gonococcus but also anaerobic and facultative bacteria. Penicillin (or ampicillin) plus an aminoglycoside is a commonly used combination,[4,13] but fails to cover Bacteroides fragilis well. An aminoglycoside plus clindamycin or chloramphenicol[36,37] provide complete coverage for all the known pathogens of PID except for group D streptococcus. Triple drug therapy utilizing penicillin, an aminoglycoside, and clindamycin or chloramphenicol[4] furnishes complete coverage against all bacteria implicated in PID.

Additional Measures

General supportive measures, such as bed rest, pelvic rest (with sexual abstinence until the pelvic examination is normal), analgesics, and hydration, are felt to be useful in the management of acute PID.[12,15] Placing the patient in a Fowler's position (head of bed up 18 to 20 inches with the knees elevated) may serve to make the patient comfortable but is of unproven benefit. Even though there is no evidence that removing an intrauterine device (if present) is beneficial, most investigators recommend that it be done.[4]

Surgical Therapy

The great majority of patients with acute PID will respond to medical management, including those with inflammatory pelvic masses.[38] With the increasing utilization of laparoscopy removing the need for exploratory laparotomy for diagnostic purposes, surgery in the primary management of acute PID is rarely indicated.[39] Nevertheless, surgical intervention is indicated in the following situations: (1) absence of clinical improvement despite adequate antibiotic therapy,[12] (2) presence of a pelvic mass that persists or enlarges despite medical management,[12,39] (3) suspected rupture or leakage of a tubo-ovarian abscess,[40] (4) evidence of intraperitoneal bleeding secondary to erosion of a major blood vessel by the infection,[40] and (5) a pointing abscess that can be drained extraperitoneally.[38] Surgical procedures employed include posterior colpotomy (reserved for midline, fluctuant abscesses that dissect the rectovaginal septum)[39] and laparotomy with excisional surgery of involved structures (adnexectomy, total abdominal hysterectomy with bilateral salpingo-oophorectomy, etc).

Prognosis

Although modern therapy has nearly eliminated the mortality directly attributable to acute PID, there is still a substantial amount of morbidity and mortality stemming from its inflammatory sequellae.

Recurrent PID

As previously mentioned, up to 23 percent of patients with one episode of PID will have a second episode.[6]

Infertility

Acute PID is felt to be a major cause of infertility in the United States. Pregnancy rates of 67 to 84 percent following gonococcal PID and 61 to 81 percent following nongonococcal PID have been

cited.[4] Westrom[6] found the risk of infertility (due to fallopian tube occlusion) to be 12.8 percent following one episode of PID, 35.5 percent after two episodes, and 75 percent following three episodes of PID. Additionally, his data revealed that the risk of infertility was approximately three times higher following an episode of nongonococcal PID compared with gonococcal PID.[6] McCormack et al[41] corroborated this latter finding and found it to be independent of the number of prior episodes of PID.

Ectopic Pregnancy

Pelvic inflammatory disease is felt to be primarily responsible for the recent tripling of ectopic pregnancies occurring in the United States.[3] It has been estimated that one episode of PID raises a woman's chances of having an ectopic pregnancy six times.[6] Pathologic changes of PID are found on laparotomy in 40 to 54 percent of cases of ectopic pregnancy.[42] In view of this, PID may be responsible for nearly one half of the maternal deaths resulting from ectopic pregnancy.[1]

Tubo-ovarian Abscess

Ginsberg et al[43] found that of 110 patients with PID and tubo-ovarian abscess who initially responded to medical therapy, 34 (31 percent) subsequently required surgery during a later hospitalization for persistence or recurrence of disease. Rupture of a tubo-ovarian abscess with peritonitis is a surgical emergency and has been associated with a mortality rate as high as 8.6 percent even with surgical therapy.[44]

Chronic Pelvic Pain

Chronic pelvic pain develops in 17 to 18 percent of patients following an episode of PID.[6,44]

Prevention

When considering the staggering economical, medical, and social consequences of PID, it is clear that more aggressive measures directed toward its prevention are required. Both private physicians and public health agencies need to make a firm commitment to the principles of epidemiological control of this disease and uniformly apply them. Such a commitment would require a general upgrading of current clinical and epidemiological services.

Treatment and Follow-Up

It is important that the clinician make an active effort to ensure that the patient complete her full course of therapy and return for a follow-up visit so that the adequacy of treatment can be assessed. Follow-up cultures for gonorrhea should be obtained seven days after completion of therapy. Since 39 to 52 percent of male contacts of women with gonococcal PID and 8 to 14 percent of contacts of women with nongonococcal PID have gonorrhea,[45] it is imperative that the sex partner(s) of all women with PID be identified, evaluated, and adequately treated.

Much of what has been said regarding the management of women with PID applies to men with urethritis as well. Contacts of men with gonococcal urethritis should be routinely treated for gonorrhea. Routine treatment of contacts of men with nongonococcal urethritis has been recommended to reduce the risk of recurrent urethritis in men as well as the risk of potential complications of chlamydial and mycoplasmal infection in women.[46,47]

Contraceptive Counseling

Barrier methods of contraception and oral contraceptives appear protective against PID and should be encouraged in eligible women with a high-risk profile for PID.[8] The intrauterine contraceptive device increases a woman's risk for PID and should be generally discouraged in women with significant risk factors for PID.

Control of Gonorrhea

Gonorrhea control programs, by reducing the incidence of gonorrhea, play a major role in the prevention of PID in the United States. Available methods for achieving control, which can be practiced by private physicians as well as public health facilities, include patient education, screening cultures in patients with a significant risk for gonorrhea, rigorous contact tracing, epidemiological treatment, and utilization of standardized treatment schedules.[2,45]

From a research standpoint, it is important that the role of Chlamydia trachomatis and the genital mycoplasmas in the pathogenesis of PID and the importance of this role in the United States be definitively defined. If, for example, C trachomatis is clearly established as an important pathogen in the United States, then epidemiologic control programs (for Chlamydia) similar to those currently applied to gonorrhea and syphilis would be mandated.

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