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Infection and Infertility

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Abstract

About 1/3rd of all women diagnosed with subfertility have a tubo-peritoneal factor contributing to their condition. Most of these alterations in tubo-ovarian function come from post-inflammatory damage inflicted after a pelvic or sexually transmitted infection. Salpingitis occurs in an estimated 15% of reproductive-age women, and 2.5% of all women become infertile as a result of salpingitis by age 35. Predominant organisms today include those from the *Chlamydia* species and the infection causes minimal to no symptoms – leading to chronic infection and consequently more damage. Again, a large proportion of patients suffering from pelvic infection contributing to their subfertility are undiagnosed to be having an infection. Chronic inflammation of the cervix and endometrium, alterations in reproductive tract secretions, induction of immune mediators that interfere with gamete or embryo physiology, and structural disorders such as intrauterine synechiae all contribute to female infertility. Infection is also a major factor in male subfertility, second only to abnormal semen parameters. Epididymal or ductal obstruction, testicular damage from orchitis, development of anti-sperm antibodies, etc are all possible mechanisms by which infection can affect male fertility.

Keywords: Infertility, Infection, pelvic inflammatory disease, salpingitis, epididymo-orchitis, antisperm antibodies

1. Introduction

The association between infection and infertility has been long known. Of all causes of female Infertility, tubal or peritoneal factors amount to about 30-40. The infections that lead to asymptomatic infections are more damaging as lack of symptoms prevents a patient from seeking timely medical intervention and consequently chronic damage to pelvic organs. Indeed, timely management of sexually transmitted or other infections goes a long way in preventing damage, disability, chronic pelvic pain, altered tubo-ovarian relationship and consequently helps in maintaining fertility.

Tubal and peritoneal pathology is among the most common causes of infertility and the primary diagnosis in approximately 30-35% of infertile couples. A history of pelvic inflammatory disease (PID), septic abortion, ruptured appendix, tubal surgery, or ectopic pregnancy suggests the possibility of tubal damage. PID is unquestionably the major cause of tubal factor infertility and ectopic pregnancies. Classic studies in women with PID diagnosed by laparoscopy have revealed that the risk of subsequent tubal infertility increases with the number and severity of pelvic infections; overall, the incidence is approximately 10-12% after one episode, 23-35% after two, and 54-75% after three episodes of acute PID.[1] The most frequent causes for pelvic infections are sexually transmitted pathogens and intrauterine manipulations like curettage, evacuation, etc.

2. Epidemiology

Approximately 35% of women with an infertility problem are afflicted with post-inflammatory changes of the oviduct or surrounding peritoneum that interfere with tubo-ovarian function. Most of these alterations result from infection. Salpingitis occurs in an estimated 15% of reproductive-age women, and 2.5% of all women become infertile as a result of salpingitis by age 35.[2] Because in most cases, especially those caused by *Chlamydia trachomatis*, signs and symptoms are often minimal or non-existent, the actual percentage of women with upper genital tract infections is probably underestimated.

Unfortunately, the impact of infectious sequelae on human reproduction continues to increase as a consequence of sexual promiscuity and the popularity of non-barrier methods of contraception. *C. trachomatis* and gonorrheal infections, as well as mixed anaerobic infections, are the most prevalent causes of upper genital tract infections resulting in pelvic inflammatory disease (PID). Bacterial vaginosis, *Trichomonas vaginalis*, and *Candida albicans* are the most prevalent bacterial, protozoan, and fungal causes of lower genital tract infections. Although gonorrheal infections have been on the decline in the last decade, chlamydial infections of the male and female genital tract continue to be an increasing problem, and *C. trachomatis* is the major cause of tubal factor infertility.[3] *C. trachomatis* is usually recovered three to five times more frequently than *Neisseria gonorrhoeae* from the reproductive tracts of infected individuals.

Women are twice as likely as men to acquire gonorrhea or *Chlamydia* during a single act of unprotected intercourse with an infected partner. Many newly infected women have no symptoms and so do not seek medical intervention and continue to spread the infection to other sexual partners. An estimated 10% to 20% of untreated women with endocervical gonorrhea or chlamydial infection eventually develop salpingitis.[4] Scholes et al[5] recommended routine testing of sexually active women to prevent sequelae like pelvic inflammatory disease and consequently infertility. Despite the current focus on sexually transmitted diseases (STDs), infertility may also follow blood-borne infections such as tuberculosis, mixed aerobic and anaerobic infections of other pelvic sites, inflammatory complications of surgical trauma, post-abortion and puerperal sepsis, and appendicular rupture.

3. Infections and male infertility

Acute and chronic genital tract infections are well-known causes of infertility in men (Table 1). Episodes of acute orchitis or epididymitis may result in permanent damage to the testis or to obstruction in the efferent ejaculatory ducts. *C. trachomatis* causes approximately 50% of epididymitis in sexually active men under age 35. Unilateral epididymal obstruction is seldom diagnosed, and its effect on fertility is largely unknown. However, 80% of men with unilateral ductal obstruction have antibodies to sperm, a potential cause of male infertility.[6] Appropriate assessment of a semen sample including tests like presence of seminal Fructose, neutral alpha-glucosidase and pH go a long way in differentiating between obstructive and non-obstructive azoospermia.

Orchitis	mumps, tuberculosis, syphilis, pancreatitis
Epididymitis	gonorrhea, tuberculosis, chlamydiae, ureaplasmas, <i>Pseudomonas</i> , coliform, and other bacterial infections
Seminal vesiculitis	tuberculosis, trichomoniasis, other bacteria
Urethritis	gonorrhea, chlamydiae, ureaplasmas, trichomoniasis

Table 1. Male Genital Tract Infections That May Cause Infertility

Most men do not develop antibodies to their own spermatozoa because the male genital tract is essentially a closed tube, and sperm are isolated from the immune system. Genital tract infections, even those without symptoms, can weaken this barrier, leading to sperm leakage and the influx of immunologically competent cells. Genital tract infections are a major cause of anti-sperm antibody formation in men.[7] Similarly, genital tract infections and anti-sperm antibody formation in men can lead to immune-mediated infertility in women.[8]

Mumps orchitis is a well-known testicular infection resulting in damage to the germinal epithelium. Systemic infections, whether bacterial or viral, may also cause depression of sperm production for variable periods. Between 2 and 6 months may be required for normal seminal cytology to reappear after a severe febrile illness. Urethral stricture is an occasional complication of untreated gonorrhea. Although the stricture does not in itself interfere with sperm motility, it may cause recurring urinary tract infection or prostatitis and epididymitis.

The fertility of a couple may be impaired if the man has a chronic bacterial prostatitis. Chronic prostatitis is presumed to be caused by a pathogenic organism and in most cases is associated with leukocytes in the semen. The prevalence of leukocytospermia among male infertility patients is about 10% to 20%. Although the exact role of WBCs in semen and its importance with respect to fertility is not clearly elucidated, there is some evidence that treating such patients with long term antibiotics does have a favourable impact on the semen parameters.[9] According to a study the presence in semen of counts more than 10,000 colony-forming units/ml had a negative effect on IVF pregnancy rates when *E. coli*, *Proteus*, or *S. aureus* organisms were isolated.[10] Again, there is some evidence that the occurrence of leucocytes in semen

yields abnormal sperm function tests, possibly because of the damaging effects of free radicles of WBCs to the sperms in their journey through the epididymis.[11] There is also substantial evidence that infection contributes to the development of sperm antibodies. Sperm antibodies have been detected in 48% of men with culture-positive asymptomatic infections, 47% of men with a history of urethritis or prostatitis, and in only 5% of men with no infection and a normal semen analysis.

The presence of IgA antibodies was associated with reduced fertility.[12] High concentrations of sperm antibodies can interfere with fertility by several mechanisms. Antibodies on sperm heads or tails may cause sperm to agglutinate. Tail-bound antibodies also interfere with sperm motility. Antibodies anywhere on spermatozoa can lead to sperm phagocytosis through binding to Fc or complement receptors on phagocytic cells. Similarly, antibody-bound sperm react with cervical mucus leading to sperm immobilization and expulsion from the female genital tract. Antibodies on sperm can interfere with sperm binding and penetration of the oocyte.[13] Similar to the situation in women, *C. trachomatis* infection of the male genital tract is often asymptomatic and therefore may persist for a long time. One study using PCR analysis of semen specimens suggested that an asymptomatic unsuspected *C. trachomatis* male genital tract infection may be the cause of previously unexplained infertility.[14] In response to a persistent asymptomatic chlamydial infection and HSP60 production, $\gamma\delta$ T cells may be induced in the male genital tract; $\gamma\delta$ T cells are capable of releasing proinflammatory cytokines and could therefore initiate an antisperm immune response within the genital tract.

4. Infections and female infertility

4.1. Pelvic inflammatory disease

PID is a common but vaguely defined complex of signs and symptoms resulting from the spread of pathogenic microorganisms from the vagina and endocervix to the uterus, body of the endometrium, and fallopian tubes. PID can also follow aseptic induced abortion or as a post-partum infection. *C. Trachomatis* salpingitis can be seen in as many as 15% patients who undergo an induced abortion. PID has reached epidemic proportions and according to the CDC, the cost of PID measured in lost earnings and money spent for health services was estimated at \$4.2 billion in 1990.[15] According to a Swedish study[16] tubal infertility occurs in approximately 11% of women who have one episode, in 23% of women who have two episodes, and in 54% of women who have three or more episodes of salpingitis. (Table 2)

As could be seen from Table 2, they found that tubal infertility is directly related to a number of factors present during the initial episode of salpingitis, which include (besides the number of episodes) the initial severity of tubal inflammation, the organisms responsible, and the occurrence of a subsequent ectopic pregnancy. The best predictor of subsequent infertility is the degree of tubal inflammation observed through the laparoscope during the acute phase. Women with a pelvic abscess have had the highest (85% to 90%) rate of subsequent infertility.[17]

Clinical Findings	Tubal Occlusion
Degree of acute inflammation at laparoscopy*	
Mild	6%
Moderate	13%
Severe	30%
Number of episodes of salpingitis*	
One	11%
Two	23%
Three or more	54%
Type of salpingitis†	
Gonococcal	9%
Nongonococcal	16%

* Westrom L: Incidence, prevalence and trends of acute pelvic inflammatory disease and the consequences of industrialized countries. Am J ObstetGynecol 135:880, 1980.

† Westrom L: Effects of acute pelvic inflammatory disease on infertility. Am J ObstetGynecol 121:707, 1975

Table 2. Factors Influencing the Frequency of Tubal Occlusion after Salpingitis

Prompt recognition and vigorous treatment reduce subsequent severe complications of salpingo-oophoritis, such as generalized pelvic peritonitis, abscess formation, and adnexal destruction. However, many patients of PID are often asymptomatic. Approximately 60% to 80% of women with acute salpingitis have a normal temperature or no white blood cell elevation. This finding correlates with the observation that most women with tubal infertility have never been treated for a recognized episode of salpingitis. Epidemiologic studies support the concept of silent PID wherein a strong link exists between serum antibodies to *C. trachomatis* and tubal factor infertility or ectopic pregnancy in patients without a history of clinical PID.[18]

4.1.1. Treatment strategies

Prompt treatment is the key in adequate eradication of the responsible organism(s) and preventing long term sequelae like hydrosalpinx, infertility, ectopic pregnancy, and chronic pelvic pain. If the patients with mild symptoms had only cervicitis or endometritis and not salpingitis, prompt treatment before the onset of salpingitis would have a major impact on preventing tubal occlusion. Failure to use doxycycline or azithromycin to inhibit *C. trachomatis* may contribute to chronic salpingitis.[19] Approximately one half of the women with an ectopic pregnancy have grossly visible tubal damage or a partial occlusion of the tubes. About 7% to 10% of pregnancies that occur after an episode of salpingitis are in an ectopic location, and women with salpingitis have a 10-fold higher rate of ectopic pregnancy than does the general population. Approximately 40% of women who have had an ectopic pregnancy are not able to achieve an intrauterine pregnancy subsequently.[20]

4.1.2. PID and HIV

A population-based study of fertility in women with human immunodeficiency virus type 1 (HIV-1) infection in Uganda demonstrated that fertility is greatly reduced in HIV-1-infected women because of a lower rate of conception and increased rates of miscarriage and stillbirth. Numerous epidemiologic studies have demonstrated that there is a synergy among bacterial and viral STDs. Bacterial STDs have been implicated in the enhancement of HIV transmission. Conversely, the immunosuppression caused by HIV worsens the clinical course of other STDs. The low prevalence and incidence of pregnancy among HIV-infected women could reflect pre-existing tubal factor infertility and higher clinical and subclinical fetal losses resulting from HIV-1 infection.[21]

Pelvic inflammatory disease that is non-tubercular in origin can be divided into gonococcal, chlamydial, and nongonococcal-nonchlamydial disease based on the results of endocervical or peritoneal fluid cultures.

4.2. Gonococcal infection

Gonococcal PID still a major cause of infertility in women in developing Asian and African countries.[22] The bacterium *N. Gonorrhea* (Figure 1) elicits a pyogenic, inflammatory reaction characterised by purulent exudates. As the organisms replicate, the ensuing local tissue damage diminishes the oxidation-reduction potential of the environment – this explains why it is common to discover co-existing pathogens. The recovery of *N. gonorrhoeae* from tubal or peritoneal fluid in acute salpingitis patients with endocervical gonorrhea ranges from 6% to 70%. Approximately one third of patients have *N. gonorrhoeae* as a sole isolate, one third have *N. gonorrhoeae* plus a mixture of aerobic and anaerobic bacteria, and one third have a mixture of aerobic and anaerobic bacteria in the cul-de-sac only.[23]

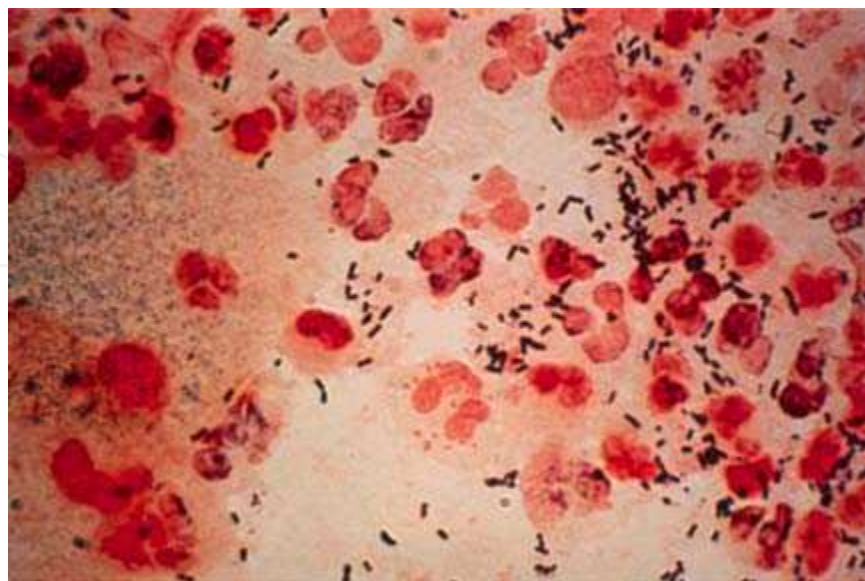


Figure 1. Neisseria Gonorrhea bacteria

N. gonorrhoeae secretes a toxin that can destroy cilia of adjacent cells in the tubal epithelium. Not only is the organism difficult to isolate from pus, but the recovery of *N. gonorrhoeae* depends on the stage of infection. The gonococcus is most frequently isolated within 2 days of the onset of symptoms and is rarely isolated if symptoms are present for 7 or more days.[24] Most symptomatic gonococcal PID cases have their onset during or just after the menses. These observations are consistent with the view that the gonococcus initiates the infection and, if the infection is not promptly treated, sets the stage for a mixed aerobic-anaerobic infection, involving pathogens that originate in the cervix and vagina.

4.3. Chlamydial infection

C. trachomatis is an intracellular bacterium that proliferates in columnar epithelial cells, where it remains protected from host immune defences by a cell membrane. It takes a longer time for *C. trachomatis* to divide (24 to 48 hours) than for classic bacteria (1 to 4 hours). There is a characteristically long time between infection and the onset of symptoms among women with *C. trachomatis*, and only mild symptoms usually occur. Widespread or systemic symptoms are unusual, although infection of the endosalpinx can produce generalized peritonitis by contiguous spread, including perihepatitis (Fitz-Hugh-Curtis syndrome).

Chlamydia appears to be a particularly important organism in infertility. There are multiple published reports in which women with tubal infertility have a 25% to 70% higher incidence of *C. trachomatis* antibody than do infertile women with normal tubes.[25] In many developed countries, *C. trachomatis* infections are now clearly the leading cause of tubal infertility. *C. trachomatis* causes the same spectrum of disease (e.g. urethritis, cervicitis, endometritis, salpingitis) as the gonococcus. *C. trachomatis* causes salpingitis more frequently than the gonococcus. Also, the degree of acute tubal damage among women with chlamydial infection equals or exceeds that observed with gonococcal infection. Women with chlamydial infection may have gonorrhea and *vice versa*.

C. trachomatis is inhibited *in vitro* by doxycycline and azithromycin but not by cephalosporins. Women with salpingitis should be treated with tetracyclines or other antibiotics that inhibit *C. trachomatis*, because cephalosporin therapy alone does not eradicate *C. trachomatis*. [26] Lack of symptoms ensures that the undetected *C. trachomatis* are able to ascend from the lower to the upper genital tract, evade the host's immune response and persist for long periods of time.

Figure 2 shows the life cycle of Chlamydia infection. Extracellular *C. trachomatis* elementary bodies (EB) infect epithelial cells. Within the cell, the EBs convert to reticulate bodies (RB), which replicate by binary fission. The RBs then convert back to EBs that are released from the cell and infect other epithelial cells. The presence of extracellular EBs activates the host's immune response, and interferon- γ is released. The interferon blocks RB replication, resulting in the formation of large, aberrant RBs. However, the RBs remain viable, and when the extracellular infection is cleared and interferon- γ is no longer present, normal RB replication resumes. These repeated cycles of replication and immune activation followed by chlamydial persistence in epithelial cells of the fallopian tube eventually lead to scar formation and tubal occlusion.[27] As has been already discussed, Witkin and co-workers found that women

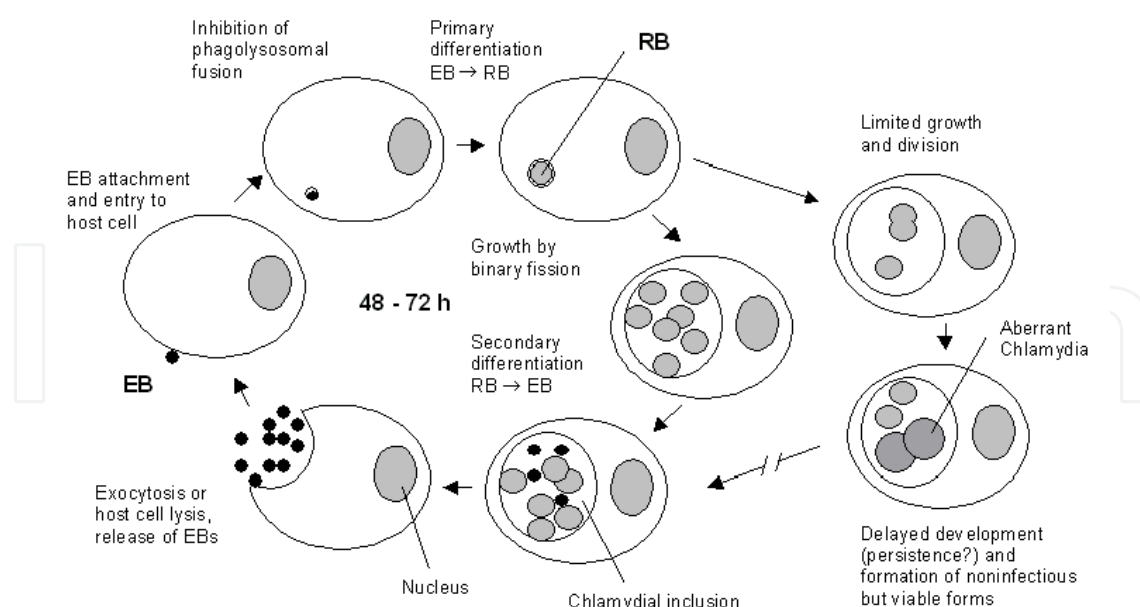


Figure 2. Effect of interferon- γ on the life cycle of *Chlamydia trachomatis*.

previously infected with chlamydia – detected by circulating systemic humoral immunity to HSP 60 had unfavourable outcomes with IVF.[18]

4.4. Nongonococcal-nonchlamydial infection

Approximately 1/4th of women with PID have a nongonococcal-nonchlamydial cause.[28] Patients with nongonococcal PID have the onset of pain distributed evenly throughout the cycle and less frequently associated with menses. There is less fever, vaginal discharge, and liver tenderness than with gonococcal PID. Despite these differences, the clinical presentation does not adequately distinguish between the two, and reliance on culture is necessary. There may be a critical number of organisms needed to breach the normally present protective host defence mechanisms and lead to infection. There is probably a continuum from bacterial vaginosis to endometritis and salpingitis, because women with bacterial vaginosis are significantly more likely to be diagnosed with PID.[29] The substantial isolation rate of bacteria other than gonococci or *C. trachomatis* from tubal fluid of these PID patients has shown that bacterial vaginosis organisms can cause acute salpingitis without antecedent chlamydial or gonococcal infection. Peritoneal or tubal cultures have yielded a mixed aerobic and anaerobic flora in 35% to 50% of patients, anaerobes alone in 15%, and aerobes alone in approximately 30% to 40% of patients. Between 4% and 17% of women with PID have had *M. hominis*, and 2% to 20%, have had *U. urealyticum* recovered from the fallopian tubes.[30]

4.5. Genital mycoplasmas and unexplained infertility

Mycoplasmas share characteristics of bacteria (they reproduce on cell-free media) and viruses (they have no cell wall and are 100 to 300 μm in diameter). Two species of mycoplasmas have

been commonly isolated from the female and male reproductive tracts: *M. hominis* and the heterogeneous group known collectively as T mycoplasma (so named for their characteristic “tiny” colonies). A distinctive property of the T strains is their ability to hydrolyze urea, and they have been named *U. urealyticum*. A third species, *Mycoplasma genitalium* has been isolated from the urethra of men and is believed to be a cause of urethritis.

Genital mycoplasmas may be of etiologic importance in nonspecific urethritis, cervicitis, and vaginitis; some cases of acute salpingitis; fever after abortions; chorioamnionitis; and puerperal infections. However, the causal role of genital mycoplasmas in infertility is still unresolved.

4.6. Genital tuberculosis

Tuberculosis continues to be endemic in many poor parts of the world like Latin America and Asia. The incidence of pelvic tuberculosis is difficult to assess as many patients are asymptomatic, therefore the disease often comes to light only incidentally during the course of investigation for a gynecological complaint. Schaefer[31] as early as in 1976 reported that 4-12% of women dying from pulmonary tuberculosis manifest evidence of genital involvement. He further mentioned that 5-10% of infertile women suffer from tuberculosis. The incidence of tuberculosis amongst women with infertility is believed to be higher in the third world countries.

The causative agent is *Mycobacterium tuberculosis* (95%) but in 5% cases it is *Mycobacterium bovis*. Genital tuberculosis almost always occurs secondary to a primary focus elsewhere, the commonest site being the lungs, but rarely from the kidneys, joints, GIT or as a part of a generalized military infection. The mode of spread is hematogenous or lymphatic and rarely from direct contiguity with an intra-abdominal organ or affected peritoneum. The fallopian tubes are affected first followed by subsequent dissemination to other genital organs – this explains the bilateral tendency of the disease. Primary genital tuberculosis is rare and possibly originates from the semen or saliva of a positive sexual partner. Tuberculosis of the cervix is present in about 5% of cases.

The leading presenting complaints in women suffering from genital tuberculosis include infertility, menstrual problems, abdominal pain, vaginal discharge and rarely genital fistulas or mass per abdomen. Sometimes general symptoms of low grade temperature, weight loss and fatigue may raise the suspicion of hitherto unsuspected tuberculosis. Classis feature is failure of fever to subside in spite of broad spectrum antibiotics. Therefore, a clinical course that is refractory to antibiotic therapy for the usual pelvic inflammatory disease should alert the physician to the possibility of tuberculosis. Pelvic examination may reveal findings like thickened adnexa which may be tender. However it may be completely normal.

Infertility is an important presenting symptom. In fact in 35-60% cases it is the only complaint. About 75% present with primary infertility and 25% give history of previous conception. These patients may or may not give a history of contact with a person suffering from pulmonary tuberculosis.

Diagnosing tuberculosis still remains a challenge. This is due to a wide variety of clinical presentation and lack of diagnostic tests with a good positive predictive and negative predic-

tive value. A single, reliable, convenient, economical test that has a good degree of sensitivity and specificity is yet to be discovered. Diagnosis still remains subjective, and is done usually at the time of laparoscopy done for evaluating infertility or chronic pelvic pain. Pathognomic sign of appearance of small tubercles all over the peritoneum that represent caseating granulomas is seen only rarely. Other findings include appearance of tubo-ovarian masses with varying degree of intra-pelvic adhesions, bead like growths or rigid lead-pipe appearance of fallopian tubes, hydrosalpingx and military white tubercles on the serosa of the uterus. Samples can be taken for acid-fast bacilli staining (Figure 3) or culture. However both methods have low sensitivity. Polymerase chain reaction is highly sensitive, but may yield false positives due to contamination of sample from air or water contaminants. Mantoux test has limited utility now.

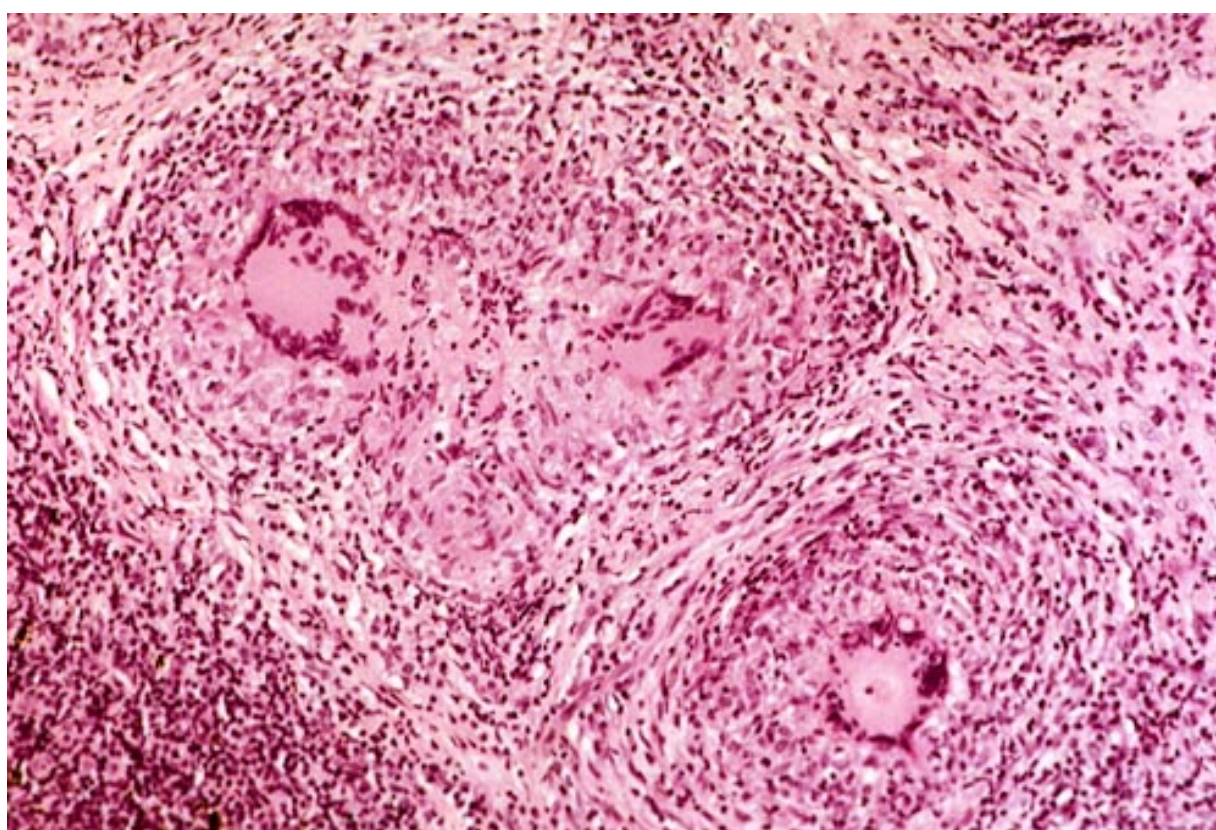


Figure 3. Typical tubercular lesion in histo-pathology

4.6.1. Treatment of tuberculosis

Extra pulmonary tuberculosis usually requires 8 to 10 months of continuous treatment particularly in developing countries to prevent emergence of multi-drug resistant tuberculosis, which is very common if treatment is given for a short period and stopped. Also, premature discontinuation of treatment may render the organisms resistant and lead to re-emergence of infection with much more severity. The therapeutic phase is divided into an intensive phase of about 2 to 4 months and continuation phase of 4 to 6 months. The two drugs used throughout

the treatment period are usually rifampicin (10 mg/kg/day, not exceeding 600 mg/d) and isoniazid (5 mg/kg/day not exceeding 300 mg). In the past the third drug used during the initial 2-4 months was Ethambutol (5-25 mg/kg/day not to exceed 2.5 gm/day) but now pyrazinamide (15-30 mg/kg/day, not to exceed 2.5 gm/day) is preferred because it does not have the ocular toxicity which is seen with ethambutol. Rifampicin is safe in pregnancy.[32] Most of these drugs are hepatotoxic and have various side effects, these have to be watched for. Surgery for the management of tuberculosis is not preferred, and reserved for special situations like persistence of an adnexal mass in spite of anti-tubercular treatment or irresponsiveness of the infection to anti-tubercular therapy.

5. Pathogenesis of PID

In gonococcal and chlamydial salpingitis, the microorganisms ascend by surface extension from the lower genital tract through the cervical canal by way of the endometrium to the fallopian tubes (Figure 4A). There can be adhesion of the mucosal folds, destruction of cilia, occlusion of the infundibulum, and production of a pyosalpinx. The gonococcal infection may spread beyond the endosalpinx, with possible focal abscess formation and perisalpingitis. In some cases of nongonococcal salpingitis, particularly with *M. hominis*,[33] the pathogens may enter through lesions in the cervix or endometrium and spread to the parametria and tubes through lymphatics and blood vessels (Fig. 4B). The inflammatory swelling that affects the parametria and the tubes is more pronounced than in gonococcal salpingitis, but the endosalpinx is usually intact.

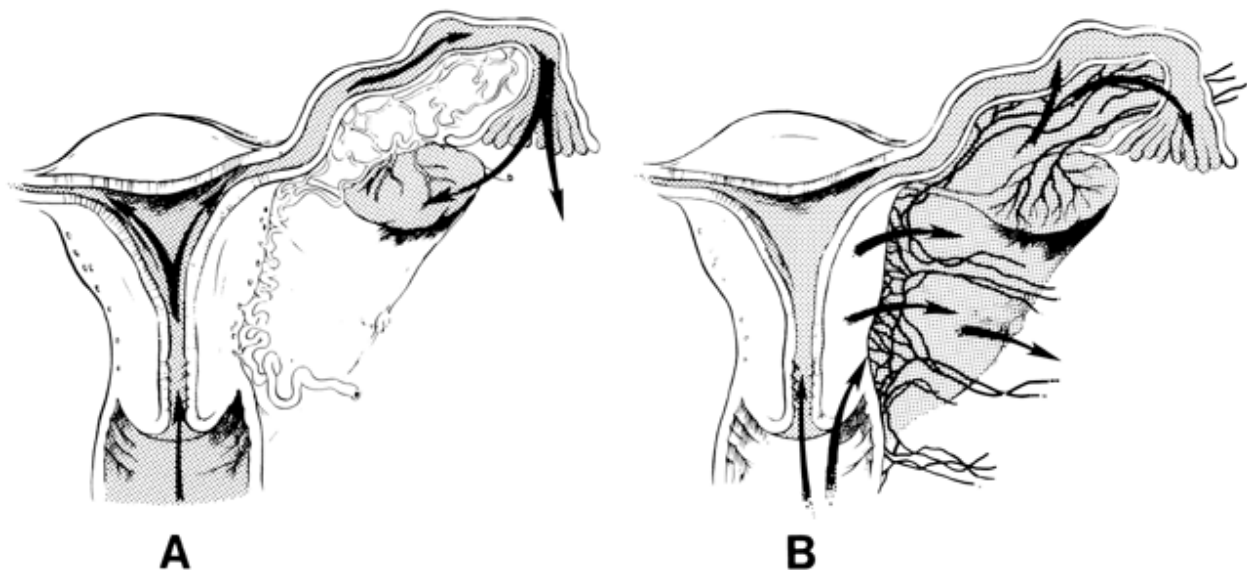


Figure 4. Pathogenesis of pelvic inflammatory disease: Schematic drawings of pathways by which genital tract infections spread. **A.** Direct spread by extension along luminal surfaces is characteristic of gonococcal and chlamydial infection. **B.** Nongonococcal bacterial and genital mycoplasma infections probably spread to the parametria and fallopian tubes primarily through lymphatics and blood vessels.

The sequelae of PID that are responsible for infertility include chronic interstitial salpingitis, hydrosalpinx, salpingitis isthmicanodosa, and periadnexal adhesions. Infertility may also occur because of abnormal secretory, ciliary, and peristaltic function of the fallopian tube. The postulated interrelationships of STDs and endogenous organisms in the pathogenesis of tubal infertility secondary to PID are depicted in Figure 5.[34]

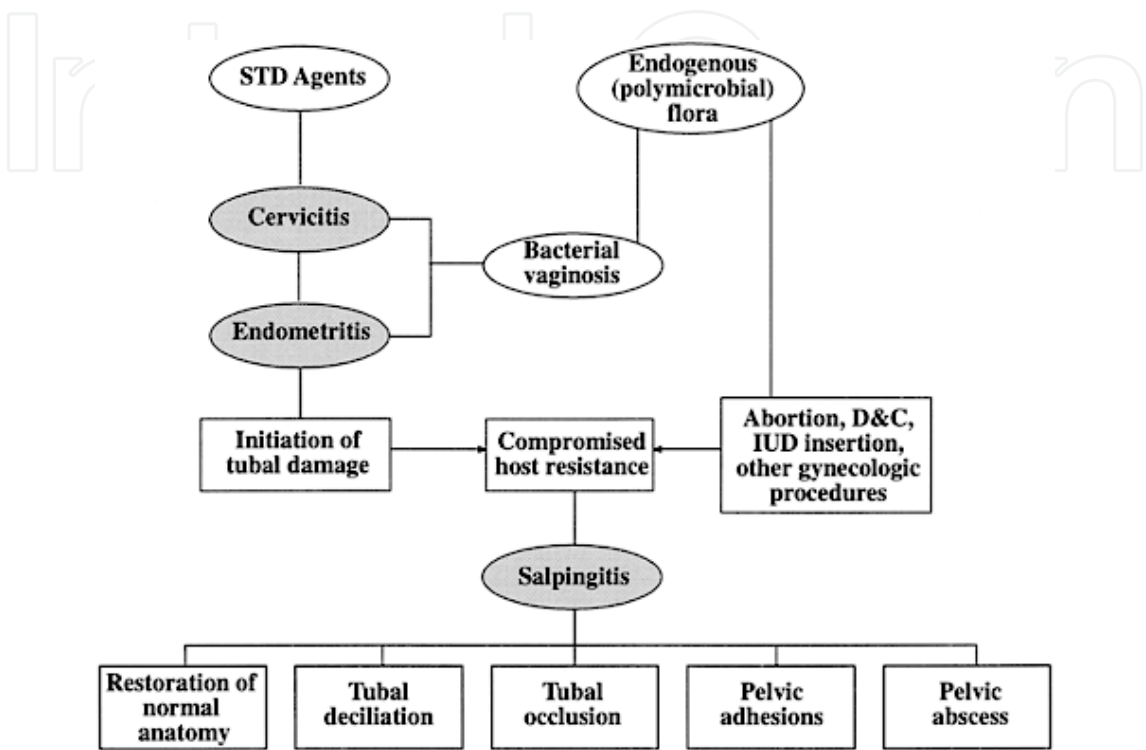


Figure 5. Postulated interactions of sexually transmitted microorganisms with endogenous lower genital tract microflora in the pathogenesis of pelvic inflammatory disease and tubal factor infertility. (Adapted from Sweet RL, Gibbs RS: Infectious Diseases of the Female Genital Tract, p 399. 3rd ed. Baltimore: Williams & Wilkins, 1995.)

6. Treatment of PID

There is controversy over the issue of outpatient versus inpatient treatment of patients with acute salpingitis. For economic and logistical reasons, most women are treated on an outpatient basis. The decision for hospitalization is usually based on the clinical severity of the illness, although criteria vary. It seems reasonable to treat major pathogens such as *N. gonorrhoeae* and *C. trachomatis* in every patient. An antibiotic regimen that takes into account the polymicrobial nature of the cause of acute salpingitis must be used. However, after treatment with different antibiotics, similar infertility rates have been found.[35] Women treated after 3 or more days of symptoms had significantly more infertility than those treated earlier.[36] Better recognition and treatment of cervicitis and endometritis before salpingitis develops is even more important in the prevention of infertility than the treatment of salpingitis *per se*. Recommended treatment schedules for uncomplicated salpingitis are shown as below:

For acute salpingitis

Parenteral Regimen A

Cefotetan 2 g, IV every 12 hours,

or

Cefoxitin, 2 g, IV every 6 hours,

plus

Doxycycline, 100 mg, IV or orally every 12 hours

Parenteral Regimen B

Clindamycin, 900 mg, IV every 8 hours,

plus

Gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing may be substituted.

Regimen A

Ofloxacin, 400 mg, orally twice each day for 14 days,

plus

Metronidazole, 500 mg, orally twice each day for 14 days.

Regimen B

Ceftriaxone, 250 mg, IM once,

or

Cefoxitin, 2 g, IM plus Probenecid, 1 g, orally in a single dose concurrently

once,

or

Other parenteral third-generation cephalosporin (e.g., ceftizoxime, cefotaxime),

plus

Doxycycline, 100 mg, orally twice each day for 14 days. (Include this regimen with one of the above regimens.)

(Centers for Disease Control and Prevention: 1998 Guidelines for treatment of sexually transmitted diseases. MMWR Morb Mortal Wkly Rep 1998;47(RR1):82–82.)

Patients with suspected abscesses or severe illness that may indicate the presence of organisms other than gonococci or chlamydiae should be hospitalized. Recommended treatment regimens inhibit not only *N. gonorrhoeae* and *C. trachomatis* but also a wide variety of aerobic and

anaerobic bacteria. For instance, parenteral clindamycin is effective against *C. trachomatis* and anaerobes.

The concomitant use of steroids with antibiotics has been thought to reduce the sequelae of salpingitis, but in a prospective study, Falk [77] could show no beneficial effect as judged by hysterosalpingography findings or subsequent laparotomy. Prevention of PID recurrence and its adverse effects on fertility also requires treatment of asymptomatic male sexual partners. In patients with postinflammatory tubal disease, pregnancy outcome has been correlated with the presence or absence of fallopian tube rugae on hysterosalpingograms. Pregnancy occurred in 61% of patients with moderate to excellent rugal patterns, whereas only 7% of patients with no demonstrable rugae conceived postoperatively.[38]

Today and in the foreseeable future, assisted reproductive technologies (ART), endoscopic surgery, and microsurgery have an important place in the management of infertility that results from tubal disease. There are some tubal causes of infertility for which surgery can offer little or no chance of success, such as after severe bilateral hydrosalpinx, multisite tubal obstruction, or in patients with extensive and dense pelvic adhesions. At the other end of the spectrum are patients who can achieve a 50% to 65% intrauterine pregnancy rate after microsurgical or laparoscopic adhesiolysis when the fimbriae are spared from disease and a male factor is not encountered.[39] In choosing between IVF and tubal surgery, the physician must compare success rates (which can be best defined by the birth of a live baby) and take into account the patient's age, presence of a male subfertility factor, the personal priorities of the couple, and the availability of expertise.

7. Early treatment and fertility preservation

The best prevention is to detect and treat early-stage asymptomatic and symptomatic infections. This can be achieved by the screening of all sexually active reproductive age women and by educating clinicians and patients on the importance of this testing. The importance of practicing safe sex methods cannot be over emphasized in public. Scholes et al found a 60% reduction in salpingitis prevalence rates when the population was screened for *C. trachomatis* infections compared to when they were not.⁵

With the advent of modern DNA amplification tests like Polymerase Chain Reaction (PCR) available very sensitive and specific testing on microbes can be done in a matter of hours. This obviates the need of many organisms as is the case with conventional cultures. Also, the newer tests are also more specific yielding a higher positive predictive value thus avoiding unnecessary treatments. Microbes like *C. trachomatis*[40], *T. vaginalis*[41], and *N. gonorrhoeae*[42] can be detected in samples obtained from the vaginal introitus, and there is no longer a requirement for a speculum examination. There have been efforts to make chlamydial and gonococcal vaccines, but not met much success.

8. Conclusion

The best hope for reducing the incidence of infertility related to infection lies in prevention and early detection and treatment of newly acquired asymptomatic or mildly symptomatic infections. The importance for the preservation of future fertility of avoiding high-risk sexual behaviour and the mandatory use of condoms must be stressed. Concomitantly, there must be an increased awareness by health care providers and consumers of the need for intensive screening using the latest and most effective molecular techniques followed by early effective treatment if positive.

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