THE EFFECTIVENESS FOR TREATMENT OF PELVIC INFLAMMATORY DISEASE ON LONG-TERM SEQUELAE

by

Gail Trautmann

BA, State University of New York at Binghamton, 1999

MA, Ball State University, 2001

Submitted to the Graduate Faculty of

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2006

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

This thesis was presented

by

Gail Trautmann

It was defended on

August 21, 2006

and approved by

Thesis Advisor:
Roberta B. Ness, MD, MPH
Chair, Department of Epidemiology
Graduate School of Public Health
Professor of Medicine, Obstetrics and Gynecology
Deparment of Medicine, School of Medicine
University of Pittsburgh

Kevin E. Kip, PhD
Assistant Professor
Department of Epidemiology
Graduate School of Public Health
University of Pittsburgh

Robert L. Cook, MD, MPH
Assistant Professor
Department of Epidemiology, Graduate School of Public Health
Department of Medicine, School of Medicine
University of Pittsburgh

THE EFFECTIVENESS OF TREATMENT ON LONG-TERM SEQUELAE OF PELVIC INFLAMMATORY DISEASE

Gail Trautmann, MS

University of Pittsburgh, 2006

Among women with pelvic inflammatory disease (PID), prevention of adverse reproductive sequelae is similarly achieved by outpatient and inpatient treatment. It is unknown if outpatient treatment is as effective as inpatient treatment among women in various subgroups based on relevant categories of age, race and clinical presentation, and if there are short-term outcomes of PID treatment that predict pregnancy, recurrent PID and chronic pelvic pain.

Women with clinical symptoms of mild-to-moderate pelvic inflammatory disease (n=831) were randomized into the PID Evaluation and Clinical Health trial, a multicenter trial of outpatient versus inpatient treatment. Comparisons between treatment groups during a mean of 84 months of follow-up were made for: pregnancies, live births, time-to-pregnancy, infertility, PID recurrence, chronic pelvic pain, and ectopic pregnancy. Outpatient treatment assignment did not adversely impact the proportion of women having any of the outcomes among women of various races; with or without previous PID; with or without baseline *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis* infection; and with or without severe PID.

In analyses of the full study cohort irrespective of random assignment, four short-term markers (pelvic tenderness at 5 and 30 days, cervical infection at 30 days, endometritis at 30 days) were evaluated in relation to long-term sequelae. Pelvic tenderness at five days (adjusted HR 1.32, 95% CI: 1.05-1.67) and at thirty days (adjusted HR 2.45; 95% CI: 1.56-3.85) significantly elevated the relative risk for developing chronic pelvic pain; tenderness at 30 days

was also significantly associated with recurrent PID (adjusted HR: 2.11; 95% CI: 1.18-3.79). However, pelvic tenderness at five days and at thirty days were poorly predictive of chronic pelvic pain or recurrent PID (positive predictive values 20.5-64.1%). In contrast to pelvic tenderness, cervical infection and endometritis at thirty days were not associated with chronic pelvic pain or recurrent PID. Moreover, none of the short-term markers significantly increased the likelihood of achieving a pregnancy. The public health significance of these findings are that women with pelvic inflammatory disease will not be adversely impacted by outpatient treatment and that no short-term marker of pelvic tenderness or infection can be predict the occurrence of PID-related reproductive morbidities.

TABLE OF CONTENTS

LIST OF TABLES

1.0 INTRODUCTION

Pelvic inflammatory disease (PID) is a common condition among reproductive aged women that results in serious gynecologic and reproductive morbidity. In a landmark long-term study that enrolled Swedish women with PID between 1960 and 1984, PID was associated with increased risk of infertility, chronic pelvic pain, recurrent PID, and ectopic pregnancy.[1-4] Subsequent smaller studies have found similar increases in risks in these long-term sequelae.[5-8]

The ability of currently recommended treatment regimens to protect against long-term sequelae after PID is largely unknown. Although the Swedish study had adequate follow-up, it did not use currently recommended anti-microbial regimens, and few subsequent studies had adequate follow-up to examine the incidence of long-term sequelae after treatment for PID. Recently, data from the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) randomized trial found no differences in the risks of long-term sequelae among women treated as inpatients or outpatients for PID.[9]

To examine the ability of treatment regimens to protect against long-term reproductive morbidity, we will address two questions. First, using the PEACH study, we will determine if there are subgroups of women for whom inpatient treatment is preferable to outpatient treatment for the prevention of long-term sequelae. It is essential to determine if there are women for whom inpatient treatment is optimal to ensure women receive the most effective treatment. Second, we will determine if women with PID with short-term markers of treatment failure (i.e.

pelvic tenderness or infection) are at higher risk of long-term sequelae than women without such markers.

This is a prospective study designed to examine the association between treatment for PID and long-term sequelae and is designed to achieve the following scientific objectives:

1. To determine if there are subgroups of women based on age, race, parity, prior history of PID, baseline cervical infection, and severity of illness status for whom inpatient treatment is more effective than outpatient treatment in the prevention of infertility, chronic pelvic pain, recurrent PID and ectopic pregnancy.

2. To determine if women with persistent cervical infection, tenderness or endometritis after treatment with current treatment regimens are at higher risk for recurrent PID, chronic pelvic pain and failure to have a live birth than women without persistent cervical infection, tenderness and endometritis.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 DEFINITION OF PID

Pelvic inflammatory disease (PID) is defined as "a spectrum of inflammatory disorders of the upper female gential tract, including any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis" by the Centers for Disease Control (CDC).[11] PID occurs after ascent of microorganisms, commonly of a sexually transmitted origin, from the vagina or cervix to the upper genital tract including the endometrium, fallopian tubes and ovaries. Symptoms of acute PID include pelvic pain, fever, chills, vaginal discharge, urinary tract infection symptoms, nausea and vomiting. The severity of symptoms varies widely and symptoms may be severe, or completely absent.[11]

2.2 EPIDEMIOLOGY OF PID

PID is a relatively common condition, affecting 8% of all women and 11% of African American women in the United States.[12] It has been estimated that annually 750,000 new cases occur in the US. and nearly two million women seek treatment for PID.[13,14] Rates in other countries are higher, with 15% of Swedish women diagnosed during their lifetime, and are higher still among developing areas, with up to 32% of an Australian Aboriginal population affected.[15,16]

2.3 ECONOMIC IMPACT OF PID

Both acute PID and its long-term sequelae place an enormous burden on the health care system. In 1998, annual US expenditures for total costs resulting from PID and its sequelae were $1.88 billion and much of these costs were associated with the long-term sequelae.[17] According to one estimate, the average per-person lifetime cost associated with PID is $2150, but these costs vary according to the specific long-term sequelae and are estimated at: $6350 for women with chronic pelvic pain, $6840 for ectopic pregnancy, and $1270 for infertility.[18]

2.4 PATHOGENESIS OF PID

PID is caused by the intracanalicular spread of several microorganisms into the endometrium and fallopian tubes.[10] Although *N.gonorrohoea* and *C. trachomatis* are the major pathogens, there is increasing evidence that microorganisms that are normally part of the vaginal flora or microorganisms that are associated with bacterial vaginosis (including anaerobes *G. vaginalis*, *Haemophilus influenzae,* enteric Gram-negative rods and *Streptococcus agalactiae*) may also play an etiologic role in the pathogenesis of PID.[19-23]

The major barriers that normally protect the upper genital tract from vaginal and cervical microorganisms are the cervical mucus plug and the endocervical canal.[24] During cervical infection, the endocervical canal is damaged and the mucus plug commonly breaks down, facilitating ascending infection.[24] Damaged ciliated epithelial cells in the endometrium and fallopian tubes that result from the infection further contribute to the ascent.[25] Westrom and Mardh proposed that *N. gonorrhoeae*, *C. trachomatis*, *M. hominis*, and other bacteria may adhere

to spermatozoa, potentially promoting ascension to the upper genital tract, although this has not been verifed.[26]

Additionally, hormonal levels and menstruation may also contribute to the ascending infection. Rising estrogen and falling progesterone levels during the mid menstrual cycle cause the cervical mucus to thin, making it more penetrable to infection; however, after ovulation, as a result of rising progesterone levels the cervical mucus thickens and again becomes less penetrable to infection.[24] Menstruation results in both the loss of the cervical mucus plug and retrograde menstruation, which can flush the infection into the upper genital tract. Further, blood provides a suitable substrate for bacterial replication. The incidence of PID may vary according to the menstrual cycle. In half of women with *N. gonorrhoeae* and/or *C. trachomatis*, the onset of pain occurred within the first seven days of menses, while for women with neither *N. gonorrhoeae* or *C. trachomatis* PID, the onset of pain occurred 14 or more days following menses.[27]

2.4.1 Role of *Neisseria Gonorrhoeae* in PID

Specific pathways vary slightly according to the organisms involved in the infection. *N. gonorrhoeae* usually spreads through a direct route from the endocervix along the endometrial surface to the tubal mucosa. Through production of IgA proteases, gonococci break down secretory IgA that normally prevents adherence to mucusoal surfaces.[28] *N. gonorrhoeae* produces several extracellular products capable of cellular damage, including phospholipase and peptidase.[25]

2.4.2 Role of *Chlamydia Trachomatis* in PID

Chlamydia trachomatis also spreads from the endocervix to the endometrium and thus fallopian tubes. However, unlike gonococcal PID, the bacterial replication of *C. trachomatis* does not produce tissue damage. Instead, tissue damage results from a host immune response, initiated by chlamydia heat shock protein (HSP). Chlaymdia HSP and human HSP are highly homologus and capable of producing an autoimmune response resulting in chronic inflammation that may cause continual damage after resolution.[29-33] In a monkey model, repeated chlamydial infections produced salpingitis that persisted until the conclusion of the 16-week observation period.[30] A later study showed that the tissue damage was provoked by immune-mediated mechanisms that included plasma cell infiltration, lymphoid follicle formation and increased fibroblast activity.[33] In a separate study in a monkey model, it was shown that Th-1 cytokines, which promote inflammatory damage and fibrosis, continued to dominate after repeated chlamydial infections and a change to dominance of Th-2 cytokines did not occur.[34] Further, using monkeys both previously inoculated and not inoculated with *C. trachomatis*, CHSP 60 produced a delayed-type hypersensitivity reaction causing tissue damage.[35,36] Additionally, HSP60 may also be a marker for persistent infection. In a study of human PID, IgA response in the serum was correlated with CHSP60 IgG response in women with PID, but not among women with acute chlamydial infection.[37] Infection and inflammation associated with chlamydia have been associated with tubal scarring, tubal obstruction, peritubal adhesions and infertility.[38-40]

2.4.3 Role of Aerobes and Anaerobes in PID

Several aerobic, anaerobic and facultative organisms have been associated with the ascent of *N. gonorrhoeae* and *C. trachomatis* to the upper genital tract and thus with the development of PID; many of these organisms are also associated with bacterial vaginosis, including *G. vaginalis*, *Haemophilus influenzae,* enteric Gram-negative rods and *Streptococcus agalactiae*.[19-23] In vitro studies have suggested that certain anaerobes, such as *Bacteroides fagilis*, can promote tubal and epithelial damage.[41] In a cross-sectional study, bacterial vaginosis was associated with nearly a three fold increase in risk for subclinical PID (OR=2.7; 95% CI: 1.02-7.2).[42] In a separate cross-sectional study, 14 of 25 women with bacterial vaginosis had upper genital tract infection, compared to 27 of 91 of women without bacterial vaginosis (p=0.015).[43] In a large three year prospective study, baseline bacterial vaginosis was not associated with the development of PID (HR = 0.89; 95% CI: 0.55-1.45).[44] However, in a separate cluster analysis of these women, being in the highest tertile of growth of bacterial vaginosis-associated organisms was associated with a two fold increase in risk for development of PID (RR=2.03; 95% CI: 1.16-3.53).[45] Aerobic and anaerobic bacteria may be secondary to upper genital tract infection with *N. gonorrhoeae* and *C. trachomatis*, where the bacteria ascend and multiply in immune compromised environments.[23]

However, upper genital tract infection has been documented in the absence of lower genital tract infection, suggesting that upper genital tract infection may persist despite lower genital tract resolution. Among 16 women with acute salpingitis treated for *C. trachomatis*, three women had positive endometrial cultures for *C. trachomatis* despite negative endocervical culture after treatment,[46] and in a separate study of 71 women with laparoscopically diagnosed PID, four women had positive abdominal cultures for *C. trachomatis* despite negative endocervical cultures.[47]

Salpingitis (inflammation of the fallopian tubes characterized by swelling of the mucosal folds and leukocyte infiltration) and endometritis (inflammation of the uterine lining characterized by leukocyte infiltration and epithelial necrosis) may develop as a result of the upper genital tract infection.[24] The inflammatory processes may cause fibrin deposits to formulate. If the infection spreads to the pelvic peritoneum, the organs may adhere to one another, potentially causing tissue destruction and tubo-ovarian abscess formation.[26]

2.5 RISK FACTORS FOR PID

Because most cases of PID result from complications of an initial sexually transmitted infection, risk factors for PID include risk factors for the acquisition of an initial infection and risk factors for the ascension into the upper genital tract. Risk factors for the acquisition of an initial infection include: greater number of current and lifetime partners, younger age at first intercourse, greater frequency of intercourse, greater rate of acquiring new partners, younger age, black or minority race, prior history of STD, prior history of PID, less education, being single or divorced, non use of barrier contraceptives, and drug and alcohol abuse.[48-51] Behavioral and socioeconomic risk factors are commonly surrogate markers of risky sexual behaviors, delay in seeking care and noncompliance with treatment. Early diagnosis and treatment are important for reducing the risk for development of PID, as it has been demonstrated that seeking care three or more days after the onset of pelvic pain was associated with a three fold increase in risk for infertility or ectopic pregnancy compared to seeking prompt care (OR=2.8, 95% CI: 1.3-6.1).[52]

Risk factors for the ascension of the infection to the upper genital tract that are independent of STD acquisition include younger age, greater parity, coitus during menstruation, recurrent infection, use of an intrauterine device and douching.[51] Younger age is associated with increased cervical ectopy, providing a greater pathogen attachment area.[24] Coitus during menstruation may allow the infection to adhere to spermatozoa and ascend into the upper genital tract.[26] IUD insertion may disrupt the vaginal mucus and flora, allowing transport of organisms to the upper genital tract.[53] Although a large randomized trial of treatment options found no relationship between IUD use and upper genital tract infection,[54] results from a meta-analysis of studies published between 1974 and 1990 showed a three fold increase in risk for symptomatic PID among IUD users compared to users of non-IUD contraception (R=3.0; 95% CI: 2.4-3.8) and a nine fold increase for asymptomatic PID among IUD users compared to users of non-IUD contraception (RR=9.2; 95% CI: 2.6-24).[55] Douching may disrupt the vaginal flora and flush the microorganisms into the upper genital tract.[48] However, results from a large randomized trial of treatment options for PID suggested that douching increases the risk for upper genital tract infection only in women with normal or intermediate flora, not in those with bacterial vaginosis. The authors suggested that douching increases the ascension of microorganisms into the upper genital tract, but because women with bacterial vaginosis may already have high movement of microorganisms, their rates of upper genital tract infection are less affected than women with normal or intermediate flora.[56]

2.6 LONG-TERM SEQUELAE OF PID

PID is associated with major reproductive and gynecologic morbidity. The acute infection leads to tubal scarring and adhesions, placing women with PID at increased risk for infertility, ectopic pregnancy, chronic pelvic pain and recurrent PID.[1,56,57] Some researchers have proposed that worldwide PID is the leading cause of infertility and may be a reason for the rise in ectopic pregnancies in the United States.[58-60]

2.6.1 Infertility

Infertility occurs in the absence of conception after one year of sexual intercourse without contraception. In a landmark long-term study of women with PID conducted in Sweden, Westrom and colleagues enrolled women with clinically suspected PID from 1960-1984. All women underwent laparoscopy and treatment; 1844 women had laparoscopic findings of PID (patients), and 657 had normal findings (controls). Mean follow-up was 13,400 person-years for patients and 3,958 person-years for controls, after which 16% of patients and 2.7% of controls were infertile, and 10.8% of patients and 0% of controls developed tubal infertility.[1] In women with at least three episodes of PID, over half became infertile.[2] Furthermore, after twelve years of follow-up, severity of PID was associated with the probability of having a live birth, where 90% of women with mild PID, 82% of women with moderate and 59% of women with severe PID achieved a live birth.[3]

However, there are several reasons why the fertility experiences of the Swedish cohort may not generalize to American women today. First, approximately 2/3 of women in the Swedish cohort were infected with *N. gonorrhoeae* or *C. trachomatis*,[3] but more recent studies

have documented lower rates of gonorrhea and/or chlamydia.[61-64] Second, the antimicrobial regimens used in the Swedish study do not concurrently protect against *N.gonorrhoeae* and *C. trachomatis* are not therapies that are currently recommended today.[65] Third, the Swedish cohort was nearly all white, but currently in the U.S., PID affects more African American women than whites, who may be at a greater risk for adverse outcomes due to higher rates of bacterial vaginosis and STDs.[66-68] Fourth, all the women in the Swedish study had documented salpingitis, but these women may not generalize to women with signs and symptoms of the disease who represent real-world clinical experience.[3] Lastly, differences among health care systems and utilization may influence results.

Within the US, in a study of 58 women with PID documented by laparoscopy and/or endometrial biopsy who were interviewed two to nine years following the index episode of PID, 19 of the 49 women (40%) not using contraception were involuntarily infertile following the index episode.[5] In another pilot study, after at least one year of follow-up for women with PID, 55.6% (10/18) were involuntarily infertile.[6] Rates of infertility in the PID Evaluation and Clinical Health (PEACH) study that randomized 831 women to inpatient or outpatient treatment were much lower. After mean follow-up period of 35 months, 71 (18.4%) of outpatients and 67 (17.9%) of inpatients were infertile (p=.85).[9]

2.6.2 Ectopic pregnancy

Ectopic pregnancy, the most common cause of maternal death, occurs when a fertilized ovum implants outside the endometrial cavity, commonly in the fallopian tubes. Among a sample of women with ectopic pregnancies, 55% reported a prior history of PID and over 30% had gross evidence of PID.[69] In a case-control study in France, confirmed PID was associated with a five

fold increase in risk for ectopic pregnancy (OR=5.4; 95% CI:4.1-7.2) and probable PID was associated with a four fold risk increase in risk for ectopic pregnancy (OR=4.4; 95% CI:2.1-9.3).[70] In a Swedish ecologic study, a reduction in the rate of PID was strongly associated with a reduction in the rate of ectopic pregnancy.[71] In the PEACH study, rates of ectopic pregnancy were lower than would have been expected based on prior literature: 1.0% among outpatients and 0.3% among inpatients (p=.37).[9]

2.6.3 Chronic Pelvic Pain

Using a definition of chronic pelvic pain of low abdominal pain lasting at least six months that required examinations and diagnostic procedures, Westrom and colleagues found that after treatment for PID 18.1% of women had chronic pelvic pain.[4] In a British study using record linkage, women hospitalized for PID were nearly ten times more likely to be subsequently hospitalized for abdominal pain during follow-up than women with control conditions (RR=9.8, no CI provided).[7]

Within the U.S., in the study of 51 women hospitalized for PID during 1985, 24% had pelvic pain for a minimum of six months after a median 37 month follow-up.[8] In a retrospective cohort study of 1,221 pregnant women, women with a prior history of PID had a 13.07 fold higher risk for chronic pelvic pain compared to women without a history of PID (95% CI: 10.09-16.04).[72] However, as women who achieved a pregnancy were less likely to have scarring and adhesions, these estimates likely underestimate the risk for chronic pelvic pain.

In the PEACH study after a mean follow-up of 36 months, 33.7% of outpatients and 29.8% of inpatients experienced chronic pelvic pain (p=0.66).[9] Among these women, chronic

pelvic pain was associated with reduced scores of physical and mental health.[73] Risk factors for chronic pelvic pain in this study included nonblack race, being married, low SF-36 mental health composite score, history of PID and smoking.[74]

2.6.4 Recurrent PID

Limited data is available concerning the risk for recurrent PID after an index episode. In the Swedish study, approximately 18% of 1,288 women with laparoscopically confirmed PID had a recurrent episode.[2] Among the retrospective cohort of 51 women hospitalized PID in 1985, 43% had a recurrent episode requiring hospitalization after a median 37 months, which was associated with nearly a two fold risk compared to women without PID (OR=1.7, 95% CI: 0.9-3.1).[8] Among women randomized to the PEACH study, 12.4% of outpatients and 16.6% (p=0.11) of inpatients experienced recurrent PID by self report during a mean follow-up of 36 months.[9]

2.7 DIAGNOSIS OF PID

The presence and severity of symptoms associated with PID vary widely and can include pelvic pain, fever, chills, vaginal discharge, urinary tract infection symptoms, nausea and vomiting.[11] Pelvic pain is the most common symptom, although it is not experienced by all women with acute PID.[75] The CDC has proposed the following minimal criteria for the diagnosis of PID: uterine or adnexal tenderness, or cervical motion tenderness.[11] To improve the specificity of the minimum criteria, additional supporting criteria have been proposed including: oral temperature $>101^0$ F, abnormal cervical or vaginal mucopurulent discharge, presence of white blood cells, elevated erythrocyte sedimentation, elevated C-reactive protein, and cervical infection with *N.*

gonorrhoeae or *C. trachomatis*.[11] Although laparoscopy is considered the gold standard for PID diagnosis, it is expensive, requires general anesthesia, may not detect subtle inflammation and is associated with additional patient burden.[75] Thus, a diagnosis of PID is commonly based on clinical findings.

2.8 TREATMENT FOR PID

Treatment for PID should be initiated in sexually active young women when the minimum criteria (uterine or adnexal tenderness, or cervical motion tenderness) is met and there is no other recognized cause for illness.[11] However, because requiring both minimum criteria may result in a low sensitivity, treatment may be warranted in patients with pelvic tenderness and signs of lower genital tract inflammation.[11] If further diagnostic tests are needed (i.e. laparoscopy), treatment should be initiated prior to additional diagnostic procedures, as delayed treatment is associated with an increased risk for long-term sequelae.[6,52]

Because of the polymicrobic nature of PID, treatment is broad-based and empiric. The CDC recommended regimens provide coverage against *N. gonorrhoeae*, *C. trachomatis*, anaerobes, Gram-negative facultative bacteria and streptococci.[11] Treatment regimens have all demonstrated short-term microbiologic success by eradicating the underlying infection(s) and clinical success by reducing the signs and symptoms associated with PID (i.e. tenderness and severity scores, fever and white blood cell count). In a 1993 metaanalysis of treatment regimens, inpatient regimens consisting of: 1) clindamycin and aminoglycoside, 2) cefoxitin and doxycycline, 3) cefotetan and doxycycline, 4) ciprofloxacin or 5) metronidazole and doxycycline were found to have pooled clinical cure rates ranging from 75-95% and microbiologic cure rates

from 71-100%.[76] The one outpatient regimen consisting of cefoxitin, probenecid and doxycycline that was included in the metaanalysis had a clinical cure rate of 95% and a microbiologic cure rate of 91%.[76]

2.8.1 Recent Treatment Advances

More recently, the PEACH randomized trial demonstrated that among women with mild-to-moderate PID, there is no different in short-term clinical improvement or long-term sequelae including infertility, recurrent PID, chronic pelvic pain or ectopic pregnancy among women treated on an inpatient or outpatient basis.[9] However, the CDC recommends hospitalization if the patient has a: surgical emergency, pregnancy, failure to respond to oral therapy, severe illness such as vomiting or high fever, tubo-ovarian abscess, or is unlikely to follow an outpatient regimen.[11]

Adequate adherence is necessary for treatment to be successful. In the PEACH study, using an Electronic Event Monitoring system that recorded the date and time of each bottle opening, the overall adherence rate was 70% (71% inpatients, 69.2% outpatients); however, only 16.9% of doses were taken within approximately 12 hours (as prescribed) of the previous dose.[77] Factors related to adherence included: working, not bleeding during or after sex and not drinking hard liquor.[77]

Adherence rates from the PEACH trial demonstrate the need to investigate shorter regimens; three studies have examined such options. First, in South Africa, a single dose of azithromycin was compared to a seven-day regimen of twice daily doxycycline (100mg). The microbiologic cure for *C. trachomatis* and *N. gonorrhoeae* was 100% for both regimens and compliance for the single therapy was 100%.[78] Second, in India, a short regimen consisting of

one tablet fluconazole (150 mg), one tablet azithromycin (1gm) and two tables of secnidazole (2 gms) was compared to a seven day course of ciprofloxacin (500 mg) and tinidazole (600 mg) and a seven day course of twice daily doxycycline (100mg) and thrice daily metronidazole (200mg). The clinical cure rates for the short dose and the seven-day doses were similar (94% vs. 96% vs. 91%, respectively).[79] Adherence rates were similarly high (94% vs. 92% vs. 87%, respectively). Third, in the U.K., azithromycin (500 mg IV single dose followed by 250 mg oral for 6 days) was compared to azithromycin and metronidazole and 21 days of two standard drug regimens (metronidazole/ doxycycline/cefoxitin/probenicid or doxycycline/amoxicillin/clavulanate). The cure rates were similarly high (97%, 98%, 95% respectively).[80] However, it is unknown how well these regimens protect against long-term sequelae.

2.8.2 Effects of Treatment on Long-Term Sequelae

Concern over fertility preservation have led some researchers to advocate for hospitalization for nulligravid teenagers and women wishing to protect their future fertility.[81] Further, the CDC recommends hospitalization for women with severe illness or an inability to respond to an oral regimen.[11] However, as hospitalization is expensive, avoiding unnecessary hospitalizations can result in significant savings. The PEACH study demonstrated no differences between inpatient or outpatient treatment in long-term sequelae including pregnancy, ectopic pregnancy, recurrent PID and chronic pelvic pain.[9] However, young, nulligravid women, or women with severe disease or a history of PID may be at a higher risk for long-term sequelae, and thus hospitalization in these cases may be warranted. Inpatient regimens may be superior for these women for two primary reasons. First, parenteral administration provides higher tissue levels against infection, [82] and second, compliance may be maximized with supervised administration,

although results from the PEACH study suggest that compliance is similar between inpatients and outpatients.[52]

There is limited evidence that despite clinical and/or microbiologic cures, negative sequelae may persist. In a study involving repeat laparoscopy, after successful treatment of chlamydia with cefoxitin and doxycycline, persistent tubal inflammation was found in eight of 11 women (73%).[76] In other studies after treatment for PID, rates of tubal scarring ranged from 33% to 45%.[1,14,47] Persistence of endometritis has been found in nine of twenty (45%) women successfully treated with minocycline.[57] Thus, despite treatment and clinical improvement, upper gential tract inflammation may persist, potentially leading to damage of the upper genital tract.[81-85] Furthermore, evidence of short-term clinical cure may not predict long-term sequelae.

Only a handful of studies have actually examined long-term infertility after treatment for PID with currently recommended anti-microbials. In one study of women randomized to clindamycin and doxycycline or to metronidazole and doxycycline, 12.5% and 43% of participants in these retrospective groups were infertile after five to seven months of follow-up.[47] In a separate small pilot study over half of women treated for PID with a variety of antimicrobials were involuntarily infertile after one year.[6] Infertility rates after treatment with cefoxitin and doxycycline among the PEACH study were 18.4% and 17.9% for outpatients and inpatients respectively after a mean 36 months of follow-up.[9] In small Finish study, where among 39 women treated with doxycycline and metronidazole, 89% achieved conception after a ten year follow-up.[86] However, because the average time to pregnancy was 38 months, many of these women may have been considered infertile at some point during follow-up. Additionally, without a true control group, we do not know if fertility after treatment were restored to levels comparable to women without PID. The Swedish study did not use antibiotic combinations that

are currently recommended by the CDC; they did not concurrently cover *N. gonorrhoeae*, *C. trachomatis* and anaerobes. [38]

2.9 SUMMARY

Pelvic inflammatory is a relatively common condition in the U.S. that results in serious reproductive and gynecologic morbidity including infertility, chronic pelvic pain, recurrent PID and ectopic pregnancy. Although several treatment regimens for PID have demonstrated short-term clinical and microbiologic cures, success is usually defined according to short-term outcomes. Thus, it remains unknown how well currently recommended treatment regimens protect against long-term sequelae. The goals of these analyses are to determine how well currently recommended treatment regimens protect against long-term sequelae associated with PID.

3.0 METHODOLOGY

3.1 SUBJECTS

All participants were enrolled in the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) randomized trial. The methods of participant selection are as follows: between March 1996 and February 1999 women ages 14-37 years were recruited from emergency departments, clinics, and sexually transmitted disease units at 7 major (over 90% of enrollment) and 6 minor clinical sites in the eastern, southern, and central regions of the US. Human subject use approval was obtained at each participating institution and all participants provided informed consent. Eligibility was based on clinically generalizable criteria that included: 1) a history of pelvic discomfort for a period of 30 days or less, 2) findings of pelvic organ tenderness (uterine or adnexal) on bimanual examination, and 3) leukorrhea or mucopurulent cervicitis or both and/or untreated, but documented gonococcal or chlamydial cervicitis. Leukorrhea was defined as white blood cells in excess of epithelial cells viewed microscopically and mucopurulent cervicitis was defined by the presence of grossly yellow/green exudate on a cervical swab.

Subjects were selected from 2941 women screened. Excluded were 346 (11.9%) women who did not meet the inclusion criteria. An additional 1080 (36.7%) women were excluded on the basis of *a priori* criteria, including 141 (4.8%) due to pregnancy; 246 (8.4%) who had taken antimicrobial agents in the preceding 7 days; 248 (8.4%) with a previous hysterectomy or bilateral salpingectomy; 51 (1.7%) with an abortion, delivery, or gynecologic

surgery in the preceding 14 days; 191 (6.5%) with suspected tuboovarian abscess or other condition necessitating surgery; 163 (5.5%) with an allergy to the study medication; 29 (1.0%) who were homeless, and 11 (0.4%) who vomited after a trial of antiemetic treatment. There were 1515 women eligible. Of these, 651 refused participation and of 864 women enrolled, 831 (54.9% of those eligible) were contacted at least once after randomization.

3.2 TREATMENT

The inpatient strategy involved intraveneous cefoxitin (2 g every 6 hours) and intravenous or oral doxycycline (100 mg twice a day) for at least 72 hours, followed by oral doxycycline (100 mg twice a day) for a total 14 day course. Outpatient treatment consisted of a single intramuscular injection of cefoxitin (2 g) plus single oral dose of probenecid (1 g), followed by oral doxycycline (100 mg twice daily) for 14 days. Participants were advised to have their partners treated and to abstain from sexual intercourse until the completion of their partners' treatment.

Random assignment to inpatient and outpatient treatment was generated by the Data Coordinating Center using random blocking stratified by clinical site. Clinical sites received assignments in sealed envelopes and opened these after enrollment and baseline data collection. The Data Coordinating Center ensured correct randomization for all participants. Neither patients nor providers were blinded to group assignment.

3.3 DATA COLLECTION

Baseline data on demographic descriptors, gynecologic and reproductive history, lifestyle habits and clinical aspects of the current illness were obtained by a standardized 20-minute interview conducted by study nurses at each center. Subsequent follow-ups conducted via telephone every three to four months elicited self-reported information about pelvic pain, pregnancy and births, signs/symptoms of PID, sexually transmitted infections, contraceptive use, pattern of sexual intercourse, and health care utilization.

Standardized physical exams were completed at five days and included tenderness assessment using the 36-point scaled developed by McCormick et al [87] nausea, vaginal bleeding, fever, pain and medication compliance. Standardized gynecologic examinations were repeated at 30 days and included, tenderness assessment, cervical swabs for detection of *N. gonorrhoeae* and *C. trachomatis* by polymerase chain detection (PCR), collection of vaginal swabs for detection of bacterial vaginosis by Gram stain and aspiration of the endometrium for detection of *N. gonorrhoeae* and *C. trachomatis*. Endometritis was defined by a modification of the Kiviat criteria, and was indicated in the presence of at least five neutrophils in the endometrial surface epithelium in the absence of menstrual endometrium, or at least two plasma cells in the endometrial stroma.

3.4 FOLLOW-UP

Participants were monitored with in person visits at 5 and 30 days. Subsequent telephone follow-ups were conducted every 3 months during the first year after enrollment and then every 4 months until June, 2004, at which point we were in contact with and obtained self-reported

follow-up information for 541 (69.1% of women still alive and consenting), representing a mean follow-up time of 84 months (range 64-100 months). The mean follow-up was almost identical among women assigned to inpatient treatment (84.2 months) and outpatient treatment (84.1 months).

3.4.1 Outcomes of Follow-Up

The primary outcomes in this analysis are three long-term outcomes: pregnancy, recurrent PID and chronic pelvic pain. Pregnancy was defined by positive urine or blood test, or doctor's diagnosis. Recurrent PID was collected via self-report and verified whenever medical records were available. As previously reported, confirmation of recurrent PID was found in 76% of medical records that could be obtained and rates of recurrent PID by self-report and medical record review were similar.[9] Chronic pelvic pain was defined as pelvic pain, measured on the Von Korff pain scale,[88] reported during at least two consecutive follow-ups, thus suggesting a minimum six month duration of pelvic pain.

3.5 ANALYTIC PLAN

3.5.1 Analytic Methods for Subgroup Analysis

Power calculations developed prior to embarking on the additional 49 months of cohort follow-up revealed that we would have acceptable power to detect differences between treatments among age, race, and clinical subgroups. For example, among women with a history of PID, assuming an outcome rate of 50% in the outpatient group, we would be able to detect as

statistically significant at > 80% power outcome rates of < 37% or > 63% that is a 26% relative difference in treatment effectiveness. Assuming an outcome rate of 25% in the outpatient group, we would be able to detect as statistically significant a relative difference between treatments of 44%. Finally, assuming an outcome rate of only 10%, we would be able to detect as statistically significant a relative difference between treatment groups of 70%. These calculations assume a 70% follow-up rate, 80% power, and a two-sided alpha of 0.05. Notably, our follow-up rate was close to 70% and study outcomes (with the exception of ectopic pregnancies) occurred at rates above 10%.

Baseline differences between groups were analyzed with the student t-test for normally distributed continuous variables, the Mann-Whitney U test for non-normally distributed continuous variables, and the χ^2 or Fisher's exact test for categorical variables. Odds ratios with 95% confidence intervals were the main indicators of association. An intention to treat principle was followed for all outcomes. Odds ratios adjusted for IUD use and bacterial vaginosis were derived from logistic regression analyses. Each model was run for a given overall outcome of interest and then within subgroups. For example, overall pregnancy was the dependent variable in one logistic model wherein inpatient versus outpatient treatment was the main independent variable. All subgroups consisting of age ($\leq$ 19, 20-24, $\geq$ 25); race (African-American, white, other); parity (nulliparous, any live birth); history of PID (any, none); evidence of gonococcal/chlamydial genital infection at baseline (none, chlamydia and/or gonorrhea); and high temperature/white blood count (WBC)/pelvic tenderness score (no, yes) were defined *a priori*. These clinical criteria were defined as presence of any of the following: oral temperature >38.3^{o} C; WBC > 15,000; or highest quartile for pelvic tenderness (score >14). Time-to-

pregnancy was analyzed using a Kaplan Meier life table analysis and was stratified on the basis of the aforementioned subgroups.

3.5.2 Analytic Methods to Determine the Relationship Between Short-Term Markers of Long-Term Sequelae

Incidence rates of pregnancy (yes/no), recurrent PID (yes/no)or chronic pelvic pain (yes/no)during follow-up by short-term marker status (Pelvic tenderness at 5 and 30 days, cervical infection at 30 days, endometritis at 30 days) were estimated by the Kaplan-Meier method. Subjects who did not experience the outcome of interest were censored at the date of last follow-up. Cox proportional hazards regression analysis was used to estimate adjusted hazard ratios of the outcomes of interest by short-term marker status. Covariates selected for adjustment included those that were significantly associated with the outcome variables and those considered of clinical or biological relevance. The proportional hazards assumption of invariant relevant risk during follow-up was assessed and found to be satisfactory. Given 725 women, the study had 80% power with a two-sided alpha to detect a hazard ratio of 0.73 for pregnancy, 1.41 for chronic pelvic pain and 1.61 for recurrent PID.

4.0 RESULTS

4.1 RESULTS FROM SPECIFIC AIM 1: SUBGROUP ANALYSIS OF LONG-TERM REPRODUCTIVE OUTCOMES

At baseline, women enrolled in the PEACH study were predominately African American (75%) and less than age 25 (65%) (Table 1). Approximately one third of participants reported a previous history of PID, and showed evidence of *N. gonorrhoeae* and/or *C. trachomatis* at baseline. At baseline, the women in the outpatient and inpatient treatment groups were similar, with the exception that women in the outpatient group were more likely to have an IUD in place and to have bacterial vaginosis.

Table 1 Baseline Characteristics of women enrolled in the PEACH study by inpatient and outpatient assignment

Baseline Characteristic (n,%)	Outpatient (n=422)		Inpatient (n=409)		P-value
Age					
≤ 19	108	25.6%	101	24.7%	P=.33
20-24	159	37.7%	174	42.5%	
≥ 25	155	36.7%	134	32.8%	
Race					
African American	315	74.6%	306	74.8%	P=.94
White	69	16.4%	64	15.6%	
Other	38	9.0%	39	9.5%	
Education					
< H.S. Graduate	161	38.3%	158	38.6%	P=.50
H.S. Graduate	151	36.0%	159	38.9%	
> H.S. Graduate	108	25.7%	92	22.5%	
History of PID	127	30.5%	124	30.6%	P=.96

Table 1-continued

Baseline Characteristic (n,%)	Outpatient (n=422)		Inpatient (n=409)		P-value
Live Births					
0	148	35.3%	143	35.0%	P=.97
1-2	197	47.0%	195	47.8%	
≥3	74	17.7%	70	17.2%	
Bacterial vaginosis*	237	65.2%	203	55.2%	P=.03
Contraception past 4 weeks[1]					
Oral contraceptives	42	11.8%	38	10.9%	P=.69
Medroxyprogesterone acetate	39	11.0%	41	11.7%	P=.75
Intrauterine device	12	3.4%	3	0.9%	P=.02
Tubal Ligation	24	6.8%	37	10.6%	P=.07
Baseline GC or CT[2]					
None	226	65.1%	213	59.2%	P=.10
Any	121	34.9%	147	40.8%	
High Temp/WBC/ Pelvic Tenderness[3]					
None	203	61.5%	211	60.3%	P=.74
Any	127	38.5%	139	39.7%	

* Eighty-four gram stains were not available
1 127 women had missing information for contraception methods
2 124 women had missing information for baseline GC/CT
3 151 women had missing information for High Temp/WBC/Pelvic Tenderness

After a mean follow up period of 84 months, the frequency of pregnancy was not significantly different by treatment group either overall or among subgroups based on race, previous history of PID, parity, baseline gonococcal and/or chlamydial genital infection, or temperature/WBC/pelvic tenderness score (Table 2). In particular, with the exceptions described below, odds ratios both without and with adjustment, were bounded by 95% confidence intervals that included the null value of 1.0. We also re-categorized women with high temperature/WBC/pelvic tenderness score, including only women in the top 10% for tenderness score, and again found no significant differences between treatment groups in this more strictly defined subgroup.

Table 2 Occurrence of a pregnancy during follow-up by treatment assignment and odds ratios (OR) unadjusted and adjusted comparing outpatient versus inpatient treatment

Baseline Characteristic (n,%)	Outpatient		Inpatient		OR	OR*	95% CI
Total	414	59.4%	403	55.6%	1.17	1.27	0.92-1.75
Age							
≤ 19	108	78.7%	99	64.6%	2.02	2.04	0.99-4.21
20-24	153	64.7%	171	69.0%	0.82	0.79	0.46-1.36
≥ 25	153	40.5%	133	31.6%	1.48	1.85	1.03-3.32
Race							
African American	311	60.5%	303	55.8%	1.21	1.31	0.90-1.91
White	67	56.7%	62	50.0%	1.31	1.62	0.71-3.67
Other	36	55.6%	38	63.2%	0.73	0.57	0.18-1.84
History of PID							
No	285	63.9%	276	57.6%	1.30	1.48	1.00-2.21
Yes	124	50.0%	123	50.4%	0.98	1.00	0.56-1.79
Parity							
0	142	59.2%	139	53.2%	1.27	1.25	0.72-2.15
≥ 1	270	59.3%	264	56.8%	1.11	1.29	0.86-1.92
Baseline GC/CT[1]							
None	221	56.1%	211	50.2%	1.27	1.27	0.82-1.97
Any	120	64.2%	145	62.1%	1.09	1.22	0.67-2.22
High Temp/ WBC/ Pelvic Tenderness							
No	201	60.7%	208	54.8%	1.27	1.26	0.80-1.99
Yes	124	56.5%	137	57.7%	0.95	1.12	0.62-2.01

[1] 124 women had missing information for baseline GC/Ct

* Adjusted for bacterial vaginosis and IUD at baseline

There were no significant differences in the frequency of live births, infertility or ectopic pregnancy either overall or within any of the subgroups (Table 3, Table 4 and Table 5).

Table 3 Occurrence of a live birth during follow-up by treatment assignment and odds ratios (OR) unadjusted and adjusted comparing outpatient versus inpatient treatment

Baseline Characteristic (n,%)	Outpatient		Inpatient		OR	OR*	95% CI
Total	414	33.3%	403	33.5%	0.99	1.06	0.77-1.49
Age							
≤ 19	108	44.4%	99	40.4%	1.18	1.08	0.57-2.02
20-24	153	39.9%	171	42.1%	0.91	0.90	0.54-1.51
≥ 25	153	19.0%	133	17.3%	1.12	1.61	0.77-3.36
Race							
African American	311	31.8%	303	34.0%	0.91	0.94	0.64-1.39
White	67	38.8%	62	25.8%	1.82	2.11	0.86-5.16
Other	36	36.1%	38	42.1%	0.78	1.00	0.33-3.04
History of PID							
No	285	36.8%	276	34.4%	1.11	1.20	0.80-1.79
Yes	124	25.8%	123	30.1%	0.81	0.89	0.46-1.71
Parity							
0	142	35.2%	139	30.2%	1.26	1.17	0.66-2.07
≥ 1	270	32.2%	264	35.2%	0.87	1.01	0.67-1.54
Baseline GC/CT[1]							
None	221	33.0%	211	29.4%	1.19	1.10	0.69-1.77
Any	120	35.8%	145	40.0%	0.84	1.05	0.59-1.87
High Temp/ WBC/ Pelvic Tenderness							
No	201	36.3%	208	32.2%	1.20	1.18	0.73-1.89
Yes	124	31.5%	137	35.0%	0.85	1.16	0.63-2.14

[1] 124 women had missing information for baseline GC/Ct

* Adjusted for bacterial vaginosis and IUD at baseline

Table 4 Occurrence of infertility during follow-up by treatment assignment and odds ratios (OR) unadjusted and adjusted comparing outpatient versus inpatient treatment

Baseline Characteristic (n,%)	Outpatient		Inpatient		OR	OR*	95% CI
Total	414	16.7%	403	20.6%	0.77%	0.88	0.59-1.32
Age							
≤ 19	108	12.0%	99	23.2%	0.45	0.51	0.22-1.19
20-24	153	15.0%	171	12.3%	1.26	1.33	0.63-2.81
≥ 25	153	21.6%	133	29.3%	0.66	0.84	0.45-1.55
Race							
African American	311	18.0%	303	19.8%	0.89	1.06	0.67-1.69
White	67	11.9%	62	25.8%	0.39	0.21	0.05-0.78
Other	36	13.9%	38	18.4%	0.71	1.31	0.29-5.87
History of PID							
No	285	13.0%	276	18.1%	0.67	0.73	0.43-1.24
Yes	124	24.2%	123	26.0%	0.91	1.12	0.57-2.18
Parity							
0	142	23.2%	139	29.5%	0.72	0.84	0.46-1.53
≥ 1	270	13.3%	264	15.9%	0.81	0.90	0.51-1.59
Baseline GC/CT[1]							
None	221	17.6%	211	21.8%	0.77	0.98	0.57-1.68
Any	120	14.2%	145	19.3%	0.69	0.68	0.31-1.49
High Temp/ WBC/ Pelvic Tenderness							
No	201	15.9%	208	19.2%	0.80	0.91	0.53-1.75
Yes	124	16.9%	137	19.7%	0.83	0.93	0.45-1.93

[1] 124 women had missing information for baseline GC/Ct

* Adjusted for bacterial vaginosis and IUD at baseline

Table 5 Occurrence of an ectopic pregnancy during follow-up by treatment assignment and odds ratios (OR) unadjusted and adjusted comparing outpatient versus inpatient treatment

Baseline Characteristic (n,%)	Outpatient		Inpatient		OR	95%CI
Total	414	1.2%	403	0.2%	4.91	0.57-42.25
Age						
≤ 19	108	0.0%	99	0.0%	--	--
20-24	153	0.7%	171	0.6%	1.12	0.07-18.04
≥ 25	153	2.6%	133	0.0%	--	--
Race						
African American	311	1.6%	303	0.3%	4.94	0.57-42.49
White	67	0.0%	62	0.0%	--	--
Other	36	0.0%	38	0.0%	--	--
History of PID						
No	285	1.1%	276	0.4%	2.93	0.30-28.30
Yes	124	1.6%	123	0.0%	--	--
Parity						
0	142	0.7%	139	0.7%	0.98	0.06-15.80
≥ 1	270	1.5%	264	0.0%	--	--
Baseline GC/CT[1]						
None	221	0.9%	211	0.5%	1.92	0.17-21.31
Any	120	0.8%	145	0.0%	--	--
High Temp/ WBC/ Pelvic Tenderness						
No	201	1.0%	208	0.5%	2.08	0.19-23.12
Yes	124	1.6%	137	0.0%	--	--

[1] 124 women had missing information for baseline GC/Ct

* Adjusted for bacterial vaginosis and IUD at baseline

We further examined time-to-pregnancy using a Kaplan Meier life table analysis for those women who became pregnant during follow up. The mean time-to-pregnancy was 37 months for inpatients and 39 months for outpatients (p=0.27). Among women with a prior history of PID, there were no differences between treatment groups in time-to-pregnancy (data not shown). Furthermore, time-to-pregnancy was not significantly different between treatments

among women of various age, race, parity, baseline gonococcal and/or chlamydial genital infection, or temperature/WBC/pelvic tenderness subgroups (data not shown).

There were no significant treatment-related differences in self-reported recurrent PID overall or among subgroups (Table 6); nor were there treatment-related differences in chronic pelvic pain either overall or among any of the study subgroups (Table 7).

Table 6 Self-reported recurrent PID during follow-up by treatment assignment and odds ratios (OR) adjusted and unadjusted comparing outpatient versus inpatient treatment

Baseline Characteristic (n,%)	Outpatient		Inpatient		OR	OR*	95% CI
Total	402	18.4%	387	24.3%	0.70	0.70	0.47-1.03
Age							
≤ 19	104	21.2%	95	29.5%	0.64	0.70	0.34-1.48
20-24	151	15.9%	166	20.5%	0.73	0.65	0.34-1.27
≥ 25	147	19.0%	126	25.4%	0.69	0.70	0.36-1.38
Race							
African American	301	20.6%	288	24.7%	0.79	0.79	0.50-1.23
White	66	15.2%	61	19.7%	0.73	0.77	0.26-2.27
Other	35	5.7%	38	28.9%	0.15	0.15	0.03-0.79
History of PID							
No	278	13.7%	264	19.7%	0.65	0.66	0.39-1.10
Yes	264	18.6%	254	25.6%	0.66	0.68	0.42-1.10
Parity							
0	136	17.6%	133	21.8%	0.77	0.74	0.37-1.47
≥ 1	264	18.6%	254	25.6%	0.66	0.68	0.42-1.10
Baseline GC/CT[1]							
None	212	18.4%	203	27.6%	0.57	0.59	0.34-1.01
Any	119	21.8%	140	22.9%	0.94	0.85	0.43-1.66
High Temp/ WBC/ Pelvic Tenderness							
No	197	16.2%	200	23.0%	0.65	0.58	0.33-1.03
Yes	119	22.7%	130	26.9%	0.80	0.89	0.45-1.77

[1] 124 women had missing information for baseline GC/Ct

* Adjusted for bacterial vaginosis and IUD at baseline

Table 7 Self reported chronic pelvic pain during follow-up by treatment assignment and odds ratios (OR) adjusted and unadjusted comparing outpatient versus inpatient treatment

Baseline Characteristic (n,%)	Outpatient		Inpatient		OR	OR*	95% CI
Total	408	44.6%	391	40.7%	1.18	1.21	0.88-1.68
Age							
≤ 19	106	36.8%	98	43.9%	0.75	0.87	0.46-1.64
20-24	151	46.4%	164	36.6%	1.50	1.33	0.79-2.23
≥ 25	151	48.3%	129	43.4%	1.22	1.46	0.83-2.57
Race							
African American	306	40.5%	295	36.9%	1.16	1.33	0.91-1.95
White	67	55.2%	59	45.8%	1.46	0.91	0.40-2.05
Other	35	60.0%	37	62.2%	0.91	1.05	0.34-3.25
History of PID							
No	282	43.6%	269	37.9%	1.27	1.37	0.93-2.04
Yes	121	47.1%	118	46.6%	1.02	0.99	0.55-1.80
Parity							
0	140	35.7%	136	34.6%	1.05	1.08	0.62-1.90
≥ 1	266	49.6%	255	43.9%	1.26	1.29	0.86-1.93
Baseline GC/CT[1]							
None	219	52.1%	204	26.6%	1.25	1.26	0.81-1.97
Any	118	37.3%	141	31.2%	1.31	1.35	0.75-2.44
High Temp/ WBC/ Pelvic Tenderness							
No	199	45.7%	199	42.2%	1.15	1.21	0.77-1.92
Yes	122	45.1%	135	37.8%	1.35	1.61	0.89-2.91

[1] 124 women had missing information for baseline GC/Ct

* Adjusted for bacterial vaginosis and IUD at baseline

4.2 RESULTS FROM SPECIFIC AIM 2: ANALYSIS TO DETERMINE IF SHORT-TERM OUTCOMES ARE RELATED TO LONG-TERM SEQUELAE

The majority of women in the sample were black (73%), younger than age 25 (65%), and had no more than a high school education (74%). Nearly one third had a previous history of PID (29%) and a slightly higher percentage had an STD at baseline (36%) (Table 8). Over half of the

women had tenderness at five days (58%); approximately 19% had tenderness at 30 days, 6% had gonococcal and/or chlamydial cervicitis at 30 days, and 41% had endometritis at thirty days.

Table 8 Baseline Characteristics

Baseline Characteristic	N (726)	%
Age		
≤ 19	179	24.7%
20-24	289	39.8%
≥ 25	258	35.5%
Race		
African American	533	73.4%
White	122	16.8%
Other	71	9.8%
Education		
< High School Graduate	267	36.8%
High School Graduate	271	37.4%
> High School Graduate	187	25.8%
History of PID*		
No	509	70.7%
Yes	211	29.3%
Live Births		
0	258	35.6%
1-2	344	47.4%
≥3	123	17.0%
Baseline GC or CT**		
None	451	64.0%
Any	254	36.0%
Tenderness 5 Days		
No	306	42.1%
Yes	420	57.9%
Tenderness 30 Days		
No	509	80.8%
Yes	121	19.2%
Endometritis 30 Days		
No	245	58.8%
Yes	172	41.2%
GC or CT Status 30 Days***		
None	410	94.9%
Any	22	5.1%

* 6 women had missing information for history of PID
** 21 women had missing information for baseline GC/CT
*** 294 women had missing information for 30 day GC/CT

Tenderness at five days (adjusted HR 1.32; 95% CI: 1.05-1.67) and at thirty days (adjusted HR 2.45, 95% CI: 1.56-3.85) were significantly associated with the occurrence of chronic pelvic pain during follow-up (Table 9). However, about half of women with tenderness at five days did not experience chronic pelvic pain (PPV=47.9%) (Table 11). Tenderness at thirty days was also sub-optimally predictive for chronic pelvic pain (PPV=64.1%). Negative predictive values for tenderness at 5 and 30 days for the outcome of chronic pelvic pain were also in the range of 62-64%.

Table 9 Prediction of Chronic Pelvic Pain and Recurrent PID from Short-Term Outcomes

Short-Term Outcome	Chronic Pelvic Pain N=309	No Chronic Pelvic Pain N=398	HR*	95% CI	Re-current PID N=141	No Re-current PID N=555	HR*	95% CI
Tenderness 5 Day	196	213	1.32	1.05-1.67	83	322	1.03	0.73-1.44
Tenderness 30 Day[1]	25	14	2.45	1.56-3.85	13	24	2.11	1.18-3.79
Cervical infection[1]	8	6	1.63	0.78-3.40	5	9	1.48	0.57-3.87
Endometritis[1]	48	71	1.05	0.72-1.52	26	91	0.80	0.50-1.28

[1] Based on 298 women with complete information for the 30 day visit
* Adjusted for: age, race, education, history of PID and live births

Tenderness at thirty days was also associated with an increased risk for recurrent PID (adjusted HR: 2.11, 95% CI: 1.18-3.79). Again, the PPV was modest (35.1%) although the negative predictive value was higher (79.1%). Tenderness at 5 and at 30 days was not significantly associated with achieving a pregnancy during the follow-up (Table 10).

Table 10 Prediction of Pregnancy from short-Term Outcomes

Short-Term Outcome	Pregnant N=411	Not Pregnant N=309	HR*	95% CI
Tenderness 5 Day	21	18	0.89	0.56-1.43
Tenderness 30 Day[1]	21	18	0.89	0.56-1.43
Cervical infection[1]	9	5	0.86	0.44-1.71
Endometritis[1]	74	46	1.22	0.89-1.67

[1] Based on 298 women with complete information for the 30 day visit

* Adjusted for: age, race, education, history of PID and live births

There were no significant associations between thirty-day cervical infection or endometritis and any of the long-term sequelae. Positive predictive values for cervical infection and for endometritis at 30 days were between 22% and 64%.

Table 11 Positive Predictive Value for Each Short-Term Outcome and Long-Term Sequelae

Short-Term Outcome	Chronic Pelvic Pain	Recurrent PID	Pregnant
Tenderness 5 day	47.9%	20.5%	57.2%
Tenderness 30 day[1]	64.1%	35.1%	53.8%
Cervical Infection[1]	57.1%	35.7%	64.3%
Endometritis[1]	40.3%	22.2%	61.7%

5.0 DISCUSSION

5.1 DISCUSSION FOR SUBGROUP ANALYSIS

Previously published results from the PEACH trial indicated that women with mild-to-moderate PID did not have worse long-term reproductive outcomes after outpatient than after inpatient treatment.[9] However, the power in that analysis was insufficient to allow for a comparison of the effectiveness of treatments among relevant subgroups of women. The current analysis was undertaken after an additional 49 months of follow-up and after power calculations supported our ability to detect clinically meaningful treatment-related differences even within subgroups. Extending our previous findings, we now report that outpatient treatment assignment did not adversely impact the occurrence of a follow-up pregnancy, live birth or ectopic pregnancy; time-to-pregnancy; infertility; PID recurrence; or chronic pelvic pain among women of various ages and races; with and without a prior birth; with or without previous PID; with or without baseline *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis* infection; and with or without high temperature/WBC/pelvic tenderness score. Ectopic pregnancy occurred rarely and more frequently in the outpatient group, albeit not significantly.

Ectopic pregnancy was a rare occurrence in PEACH participants, reported by less than 1% of women, a surprisingly low rate,[11,55] which may explain why ectopic pregnancies were detected only in the dominant racial group in the study: African-American women. Explanations for the greater, albeit non-significant, occurrence of ectopic pregnancy among women assigned

to outpatient treatment are two-fold. First, a likely possibility is that a limited number of observations created unstable estimates. Second, intravenous antibiotic therapy, characterizing the inpatient treatment strategy, may have more effectively reduced ectopic pregnancy. We believe this is unlikely, however, as it assumes some pathophysiologic mechanism independent of that involved in outcomes not different between treatments, such as infertility.

Older women were statistically significantly more likely to become pregnant after outpatient treatment. However, older women assigned to outpatient treatment had neither a statistically greater likelihood of live births nor a statistically lower likelihood of infertility. Thus, we infer that this single statistically significant finding is probably a function of multiple comparisons.

The lack of treatment-related difference in multiple reproductive outcomes and among subgroups of women strengthens our previous null findings.[9] The lack of statistical difference between treatment groups might be interpreted as a poor outcome in both groups or as a good outcome in both groups, but neither interpretation can be verified in the absence of a control group without PID. Currently, the CDC recommends hospitalizing women with PID based on health-care provider discretion and in the following situations: surgical emergencies, pregnancy, failure to respond to oral antimicrobial therapy, inability to tolerate outpatient therapy, and tubo-ovarian abscess.[29] Women with these conditions were excluded from the PEACH trial so in these situations, we can make no inference about appropriate treatment. However, the CDC also suggests that women with severe illness be hospitalized. As the CDC does not define "severe illness", we used as surrogate measures an elevated oral temperature, WBC, or abdominal tenderness score, and found no treatment-related differences in outcomes among women with these clinical presentations.

Older CDC recommendations and some researchers advocate treatment of nulligravid women and teenagers as inpatients. Again, our results do not demonstrate that inpatient treatment enhances preservation of reproductive health in these relatively large subgroups of patients.

There were numerous strengths of this study. The randomization resulted in a similar distribution of most baseline characteristics between the treatment groups, thereby limiting confounding. The unequal distribution of IUD and bacterial vaginosis would have been expected to disadvantage outpatients with respect to reproductive outcomes and thereby could not have accounted for our inability to demonstrate excesses in adverse outcomes among women assigned to outpatient treatment. Moreover, we adjusted for IUD use and bacterial vaginosis in calculating risk estimates. Study generalizability was enhanced by inclusion of women with mild-to-moderate PID, who comprise approximately 90% of women with PID.[27] Finally, outcomes consisted of important long-term reproductive events, the sequelae that with treatment we are ultimately attempting to prevent.

The greatest potential limitation of subgroup analyses in the PEACH study is the inability to detect small treatment-related differences. Despite additional follow-up and a larger number of endpoints, we could generally, but not always, detect relative differences in the range of 26-70%. Other limitations include the lack of universal documentation of tubal obstruction among women with infertility, and self-reported documentation of all outcomes, which, despite our attempts to validate endpoints, remains a *caveat* to interpretation of results. Additionally, the cohort largely involved low-income African American women, who represent only one component of all women with PID. Finally, because there was no external comparison group,

we do not know if treatment restores fertility to levels comparable to women without a history of PID.

Our current findings reinforce our previous conclusion that, without evidence of unfavorable effectiveness, large cost-savings accrued by treating women outside the hospital favor outpatient management. In the original comparison of outpatient versus inpatient treatment from the PEACH Study, the PEACH authors estimated that by switching 85,000 women per year from inpatient to outpatient treatment, annual cost savings might be in the neighborhood of $500 million.[9] With the possible exception of an excess of rarely-occurring ectopic pregnancy among women treated as outpatients, in no relevant subgroups and for no adverse reproductive outcomes, could we find a disadvantage in using outpatient treatment for PID.

5.2 DISCUSSION FOR RELATIONSHIP BETWEEN SHORT-TERM OUTCOMES AND LONG-TERM SEQUELAE

The success of treatment for PID is generally gauged by short-term clinical improvement and/or microbiologic cure. Our results show that these short-term markers (tenderness at 5 and 30 days; gonococcal/chlamydial cervicitis at 30 days; endometritis at 30 days) are not strongly predictive of the long-term sequelae from PID that treatment is trying to prevent. Although persistent tenderness significantly increased the occurrence of chronic pelvic pain and recurrent PID, positive predictive values were too low to make short-term tenderness a clinically meaningful intermediate for predicting these long-term outcomes. Moreover, cervicitis and endometritis were not significantly associated with chronic pelvic pain or PID, and none of the short-term measures were predictive of the ability to achieve pregnancy.

We considered several explanations for our findings. First, cervical infection status may not adequately represent fallopian tube infection.[9,46,47] Cervical infection often exists in the absence of endometrial infection/inflammation. The converse is also true: in two studies, 3.7% to 10% of women were documented with positive upper genital tract chlamydial cultures, despite negative cervical culture at baseline.[9,47] This has also been documented post-treatment for PID, where four of 16 women had positive endometrial cultures for chlamydia despite negative endocervical cultures after second and third generation cephalosporin treatment.[30] Thus, despite a negative test for thirty day cervical infection, women may have experienced a persistent infection in their upper genital tract that contributed to long-term sequelae. The converse is also true: cervical infection often exists in the absence of endometrial infection/inflammation resulting in a false positive short-term indicator.

Second, women who delay seeking treatment for PID for three days or more are at nearly a three fold increase in risk for impaired fertility,[52] suggesting that early treatment administration may be necessary to halt a complete mounting of the inflammatory response. Because the majority of women in the PEACH study presented with three or more days of pelvic pain (71%),[9] they may have been at increased risk for long-term sequelae regardless of short-term treatment response. Our data suggest that short-term markers do not adequately reflect the underlying pathophysiology that leads some women to have adverse long-term outcomes while others do not.

Third, women may have had prior subclinical (silent) PID that resulted in tubal damage preceding the baseline episode. Prior PID may have contributed, independent of the short-term markers from the index diagnosis of PID, to adverse reproductive sequelae. In a macaque monkey model, repeated exposure to chlamydial infections produced a Th-1 type cytokine

response that was associated with the progression to fibrosis and infertility.[33-35] One test of cervical infection at thirty-days would not capture the women who had repeated exposures sufficient to produce fibrosis and scarring.

Fifth, PID has a polymicrobial etiology and several non-chlamydial, non-gonorrheal pathogens have been implicated, including *Mycoplasma hominis*, *Ureaplasma urealyticum*, bacterial vaginosis (independent of gonorrhoea or chlamydia), and *Mycoplasma genitalium*.[23,47-49] Some of these pathogens (*M. hominis* and *U. urealyticum*) are largely resistant to tetracyclines, and may have persisted following PID treatment.[52] In a previous PEACH analysis, women with nongonococcal bacteria in the endometrium were more likely to have reproductive morbidity compared to women with endometrial gonococcal infection (infertility rates were: *N. gonorrhoeae* 13%, *C. trachomatis* 19%, anaerobic bacteria 22%, *U. urealyticum* 41% and *M. hominis* 54%).[53] Further, Brunham and colleagues demonstrated over a five to seven month follow-up, 54% of women with non-gonorrheal infections had adverse reproductive outcomes, compared to none of the women with gonorrheal PID.[23] Thus, women in the study may have had non-gonorrhoeal, non-chlamydial pathogens that resulted in long-term sequelae.

One final explanation for the lack of association between short-term markers and long-term sequelae may result from the mild-to-moderate severity of the PID studied. Severe and recurrent PID was eight times more likely to fail to have a live birth in a twelve year follow-up compared to women with mild PID who had a single only episode.[2] Thus, among a sample of women with severe PID, short-term intermediates may be more strongly associated with long-term sequelae.

This is the first study to examine the associations between short-term markers and long-term sequelae related to PID. The study has several strengths. First, the prospective design

allowed actual measurements of all outcomes. Second, the PEACH study had a long-follow up duration (average follow-up length 84 months) and a sizeable rate of retention (69.1%).[9] Third, the study was generalizable, as it enrolled women with mild-to-moderate PID who comprise 90% of women with PID.[55] Fourth, standardized laboratory procedures minimized bias and misclassification.

One notable weakness is the diminution in sample size between the five and thirty day visit, with 725 women (out of 831) returning for the five day visit, and only 348 women with complete information for the thirty day visit. Lack of significant findings may have resulted from a lack of power. The women who did not return for the thirty day visit were more likely to be 25 or older, and of race other than African American or white. There were no significant differences in educational status, history of PID, parity and baseline gonorrheal/chlamydial status. A second weakness was the reliance on self-report to determine recurrent PID. However, as previously noted, we found 76% confirmation of recurrent PID in verified medical records.[9]

Short-term intermediate endpoints are frequently used to determine clinical or microbiologic cure for PID. However, our results suggest that such markers are generally unrelated to long-term reproductive morbidity and even when significant associations exist, the accompanying positive and negative predictive values are less than optimal and thus not clinically useful. When conducting treatment trials, there are no short-term markers that we examined that can be used to predict the occurrence of PID-related reproductive morbidity. Future research should determine if there are other available markers such as non-gonorrhoeal/non-chlamydial infection status, CHSP 60 that can be used to predict long-term reproductive morbidity.

6.0 APPLICATIONS TO PUBLIC HEALTH

Describing the relationships between PID and long-term sequelae contributes new insight into the complex public health challenges relating to adequate treatment for PID and for long-term sequelae consisting of infertility, chronic pelvic pain, ectopic pregnancy and recurrent PID. This thesis adds valuable information to emerging literature pertaining to PID.

First, this is the first work to examine long-term sequelae of PID among subgroups of women based on age, race, parity and clinical presentation among any population in the world. Providing evidence that all women can be treated as outpatients for PID will enable health care providers to treat women with effective methods at a lower cost and burden to the health care system.

Second, this work contributes important information concerning the role of short-term treatment markers in predicting long-term sequelae of PID. As we found no short-term markers of treatment that are associated with significantly altered risk for long-term sequelae, we cannot recommend any markers to be used in future research. Thus, to adequately determine long-term sequelae of PID, future research cannot use a short-term design.

BIBLIOGRAPHY

1. Westrom L, Joesoef R, Reynolds G, Hagdu A, Thompson SE. Pelvic inflammatory disease and fertility. A cohort study of 1,844 women with laparoscopically verified disease and 657 control women with normal laparoscopic results. Sex Trans Dis 1992;185-192.

2. Lepine LA, Hillis SD, Marchbanks PA, Joesoef R, Peterson HB. Severity of pelvic inflammatory disease as a predictor of the probability of live birth. Am J Obstet Gynecol 1998;178:977-81.

3. Westrom L, Eschenbach D. Pelvic inflammatory disease. In: Sexually Transmitted Diseases. (3rd Edition). Holmes KK, Sparling PF, mardh PA, et al. Mc Graw Hill, New York, NY: 1999.

4. Westrom LR, Joesoef R, Reynolds G, Hagdu A. Pelvic inflammatory disease and fertility. Sex Transm Dis 1992;19:185-192.

5. Pavletic AJ, Wolner-Hassen P, Paavonen J, Hawes SE, Eschenbach DA. Infertility following pelvic inflammatory disease. Infect Dis Obstet Gynecol 1999;7:145-152.

6. Soper D, Ness RB. Pelvic inflammatory disease and involuntary infertility: prospective pilot observations. Inf Dis Obstet Gynecol 1995;3:145-148.

7. Buchan H, Vessey M, Goldcare M, Fairweather J. Morbidity following pelvic inflammatory disease. Brit J Obstet Gynecol 1993;100:558-562.

8. Safrin S, Schachter J, Dahrouge D, Sweet RL. Long-term sequelae of acute pelvic inflammatory disease. 1992;166:1300-1305.

9. Ness RB, Soper DE, Holley RL, Peipert J, Randall H, Sweet RL, Sondheimer SJ, Hendrix SL, Amotegui A, Trucco G, et al. Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease: Results from the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) Randomized Trial. Am J Obstet Gynecol 2002;186:929-937.

10. Cutter GR, Burke GL, Dyer AR, Friedman GD, Hilner JE, et al. Cardiovascular risk factors in young adults the CARDIA baseline monograph. Cont Clin Trials 1991;12:1S-77S.

11. Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. MMWR Morb Mortal Wkly Rep 2002;51:1-77.

12. National Survey of Family Growth; Vital and Health Statistics. Hyattsville (MD): US Department of Health and Human Services, Public Health Service, National Center for Health Statistics; 1995.

13. Westrom L. Incidence, prevalence, and trends of acute pelvic inflammatory disease and its consequences in industrialized countries. Am J Obstet Gynecol 1980;138:880-892.

14. Blout JH. Reynolds GH, Rice RJ. Pelvic Inflammatory Disease: incidence and trends in private practice. MMWR 32;27:SS.

15. Westrom L. Decrease in incidence of women treated in hospital for acute salpingitis in Sweden. Genitourinary Medicine 1988;64:59-63.

16. Kildea S, Bowden FJ. Reproductive health, infertility and sexually transmitted infections in indigenous women in a remote community in the Northern Territory. Australian & New Zealand Journal of Public Health 2000;4:38-386.

17. Rein DB, Kassler WJ, Irwin KL, Rabiee L. Direct medical cost of pelvic inflammatory disease and its sequelae: decreasing, but still substantial. Obstet Gyencol 2000; 95:397-402.

18. Yeh JM, Hook EW, Goldie SJ. A refined estimate of the average lifetime cost of pelvic inflammatory disease. Sex Trans Dis 2003;30:369-378.

19. Sellors J, Mahony JB, Chesnesky MA, Rath DJ. Tubal factor infertility: an association with prior chlamydial infection and asymptomatic salpingitis. Fertil Steril 1988;49:451-457.

20. Miettinen AK, Heinonen PK, Teisala K, Hakkarainen K, Punnonen R. Serologic evidence for the role of chlamydia trachomatis, Neisseria gonorrhoeae, and mycoplasma hominis in the etiology of tubal factor infertility and ectopic pregnancy. Sex Trans Dis 1990; 17:10-14.

21. Walker CK, Workowski KA, Washington AE, Soer D, Sweet RL. Anaerobes in pelvic inflammatory disease: implications for the Centers for Disease Control and Prevention's guidelines for treatment of sexually transmitted diseases. Clin Infect Dis 1999;28:S29-36.

22. Peipert JF, Montagno AB, Cooper AS, Sung CJ. Bacterial vaginosis as a risk factor for upper genital tract infection. Am J Obstet Gynecol 1997;177:1184-7.

23. Soper DE. Pelvic inflammatory disease. Infect Dis Clin North Am 1994;321-40.

24. Sweet RL. Microbial etiology of pelvic inflammatory disease. In DV Landers and RL Sweet, eds. Pelvic inflammatory disease. Spring-Verlang, New York 30-59.

25. Rice PA, Schachter J. Pathogenesis of pelvic inflammatory disease. JAMA 1991;266:2587-2593.

26. Westrom L and Mardh PA. Acute pelvic inflammatory disease (PID). In KK Holmes, PA Mardh and PF Sparling eds Sexually Transmitted Diseases, 2nd Ed. McGraw Hill, company New York. 1990. 593.

27. Eschebach DA. Epidemiology of pelvic inflammatory disease. In DV Landers and RL Sweet, eds. Pelvic inflammatory disease. Spring-Verlang, New York 30-59.

28. Mulks MH, Plaut AG. IgA protease production as a characteristic distinguishing pathogenic from harmless Neisseria. N Eng J Med 1978;299:973-976.

29. Patton DL, Halbert SA, Kuo CC, Wang SP, Holmes KK. Host response to primary *Chlamydia trachomatis* infection of the fallopian tube in pig-tailed monkeys. Fertil Steril 1983;40:829-840.

30. Patton DL, Kuo CC, Wang SP, Halbert Sa. Distal obstruction induced by repeated *Chlamydial trachomatis* salpingeal infection in pig-tailed macaques. J Infect Dis 1987;155:1292-1299.

31. Patton DL, Landers DV, Schachter J. Experimental *Chlamydia trachomatis* salpingitis in mice: Initial studies on the characterization of the leukocyte response to chlamydia infection. J Infect Dis 1989;159:1105-1110.

32. Patton DL, Wang SP, Sternfield MD, et al. Chlamydial infection of subcutaneous fimbrial transplants in cynomolgus and rhesus monkeys. J Infect Dis 1987;155:229-235.

33. Patton DL, Kuo CC. Histopathology of *Chlamydia trachomatis* salpingitis after primary and repeated infections in the monkey subcutaneous pocket model. J Reprod Fertil 1989;85:647-655.

34. Van Voorhis WC, Barrett LK, Cosgrove Sweeney YT, Kuo CC, Patton DL. Repeated *Chlamydia trachomatis* infection of *Macca nemestrina* fallopian tubes produces a Th-1 like cytokine response associated with fibrosis and scarring. Infect Immun 1997;65:2175-2182.

35. Patton DL, Cosgrove Sweeney YT, Kuo CC. Demonstration of delayed hypersensitivity in *Chlamydia trachomatis* salpingitis in monkeys: apathogenic mechanism of tubal damage. JID 1994;169:680-683.

36. Lichtenwalner AG, Patton DL, Van Voorhis WC, Cosgrove Sweeney YT, Kuo CC. Heat shock protein 60 is the major antigen which stimulated delayed-type hypersensitivity reaction in the macaque model of *Chlamydia trachomatis* salpingitis. Infect Immun 2004;72:1159-1161.

37. Clamm P, Honey L, Peeling RW, Jessaminine P, Toye B. The presence of serum antibody to the chlamydial heat shock protein (CHSP60) as a diagnostic test for tubal factor infertility. Fertil Steril 1997;67:501-504.

38. Fedele L, Acaia B, Ricciardiello O, Marchini M, Benzi-Cipelli R. Recovery of *Chlamydia trachomatis* from the endometria of women with unexplained infertility. J Reprod Med 1989;34:393-396.

39. Punonen R, Terho P, Nikkanen V, Meurman O. Chlamydial serology in infertile women by immunoflourescence. Fertil Steril 1979;31:656-659.

40. Sellors JW, Mahoney JB, Chernesky MA, Rath DJ. Tubal factor infertility: an association with prior chlamydial infection and asymptomatic salpingitis. Fertil Steril 1988;49:451-457.

41. Soderberg G. Lindberg AA. Nord CE. Bacteroides fragilis in acute salpingitis**.** Infection 1979*;* 7:226-30.

42. Weissenfeld HC, Hillier SL, Krohn MA, Amortegui AJ, Heine RP, Landers DV, Sweet RL. Lower genital tract infection and endometritis: insight into subclinical pelvic inflammatory disease. Obstet Gynecol 2002; 100:456-463.

43. Peipert JF, Montagno AB, Cooper AS, Sung JC. Bacterial vaginosis as a risk factor for upper genital tract infection. Am J Obstet Gynecol 1997;177:1184-1187.

44. Ness RB, Hillier SL, Kip KE, Soper DE, Stamm CA, McGregor JA, et al. Bacterial vaginosis and risk of pelvic inflammatory disease. Obstet Gynecol 2004;104:761-769.

45. Ness RB, Kip KE, Hillier SL, Soper DE, Stamm CA, Sweet RL, Rice P, Richter HE. A cluster analysis of bacterial vaginosis-associated microflora and pelvic inflammatory disease. AM J Epidemiol 2005; 162:585-590.

46. Sweet RL, Schachter J, Robbie MO. Failure of ß-Lactam antibiotics to eradicate *Chlamydia trachomatis* in the endometrium despite apparent clinical cure of acute salpingitis. JAMA 1983;250:2641-2645.

47. Brunham RC, Binns B, Guijon F, et al. Etiology and outcome of acute pelvic inflammatory disease. J Infect Dis 1988; 158;510.

48. Padian NS, Washington AE. Risk factors for pelvic inflammatory disease and associated sequelae. In DV Landers and RL Sweet, eds. Pelvic inflammatory disease. Spring-Verlang, New York 21-29.

49. Jamieson DJ, Duerr A, Macaset MA, Peterson HB and Hillis SD. Risk factors for a complicated clinical course among women with pelvic inflammatory disease. Inf Dis Obstet Gynecol 2000;8:88-93.

50. Simms I, Stephenson JM. Pelvic inflammatory disease; what do we know and what do we need to know? Sex Transm Inf 2000;76:80-87.

51. Beigi RH, Wiesenfeld HC. Pelvic inflammatory disease: new diagnostic criteria and treatment. Obstet Gynecol Clin North America 2003;777-793.

52. Hillis SD, Joesoef R, Marchbanks PA, Wasserheit JN, Cates W, Westrom L. Delayed care of pelvic inflammatory disease as a risk factor for impaired fertility. Am J Obstet Gynecol 1993;168:1503-1509.

53. Padian NS, Washington AE. Pelvic inflammatory disease. A brief overview. AEP 1994;4:128-132.

54. Ness RB, Soper DE, Holley RL, Peipert J, Randall H, Sweet RL, Sondheimer SJ, Hendrix S, et al. Hormonal and barrier contraception and risk of upper genital tract disease in the PID evaluation and clinical health (PEACH) study. Am J Obstet Gyencol 2001;185:121-127.

55. Gareen IF, Greenland S, Morgenstern H. Intrauterine devices and pelvic inflammatory disease: meta-analysis of published studies, 1974-1990. Epidemiol 2000;11:589-597.

56. Ness RB, Soper DE Holley RL, Peipert J, Randall H, Sweet RL, et al. Douching and endometritis. Results from the PID evaluation and clinical health (PEACH) study. Sex Transm Dis 2001;28:240-245.

57. Cates W, Rolfs RT, Aral SO. Sexually transmitted diseases, pelvic inflammatory diseases, and infertility: an epidemiologic update. Epid Rev 1990;12:199-200.

58. Cates W, Farley TMM, Fowe PJ. Worldwide patterns of infertility: is Africa different? Lancet 1985;2:596-8.

59. Ory HW. The women's health study; ectopic pregnancy and intrauterine contraceptive devices: new perspectives. Am J Obstet Gynecol 1981; 57:137.

60. World Health Organization: Infections, pregnancies and infertility: perspectives on prevention. Fertil Steril 1987;47:964.

61. Arrendondo JL, Diaz V, Maradigue GE, Oyarzun E, et al. Oral clindamycin and ciprofloxacin versus intramuscular ceftriaxone and oral doxycycline in the treatment of mild-to-moderate pelvic inflammatory disease in outpatients. Clin Infect Dis 1997;24:170-8.

62. Gogate A, Brabin L, Nicholas S, et al. Risk factors for laparoscopiclly confirmed pelvic inflammatory disease: findings from Mumbai (Bombay), India. Sex Trans Inf 1998;74:426-432.

63. Brabin L, Gogate A, Karande A, et al. Reproductive tract infections, gynaecological morbidity and HIV seroprevalence among women in Mumbai India. World Health Organization 1998;277-287.

64. Peipert JF, Boardman L, Hogan WJ, et al. Laboratory evaluation of acute upper genital tract infection. Obstet Gynecol 1996;87:730-6.

65. Westrom L, Iosif S, Svensson L, Mardh PA. Infertility after acute salpingitis: results of treatments with different antibiotics. Curr Thera Res 1979;26:752-9.

66. Hawes SE, Hillier SL, Benedetti J, et al. Hydrogen peroxide-producing lactobacilli and acquisition of vaginal infections. J Infect Dis 1996;174:1058-63.

67. Royce RA, Jackson TP, Thorp JM, et al. Race/Ethnicity, vaginal flora patterns and pH during pregnancy. Sex Trans Dis 1999;26:96-102.

68. Aral SO, Mosher WD, Cates W. Self-reported pelvic inflammatory disease in the United States, 1998. JAMA 1991;2570-3.

69. Helvacioglu A, Long EM, Yang SL. Ectopic pregnancy. An eight-year review. J Reprod Med 1979;22:87-92.

70. Bouyer J, Coste J, Shojaei T, Pouly J-L, Fernandez J, Berbaud L, Job-Spira N. Risk factors for ectopic pregnancy: a comprhensive analysis based on a large case-control population-based study in France. Am J Epidemiol 2003;185-194.

71. Kamwendo F, Forslin L, Bodin L, Danielsson D. Epidemiology of ectopic pregnanc during a 28 year period and the role of pelvic inflammatory disease. Sex Transm Inf 2000;76:28-32.

72. Heisterberg L. Factors influencing spontaneous abortion, dyspareunia, dysmenorrhea and pelvic pain. Obstet Gynecol 1993;81:594-597.

73. Haggerty CL, Schulz R, Ness RB. Lower quality of life among women with chronic pelvic pain after pelvic inflammatory disease. Obstet Gynecol 2003;102:934-939.

74. Haggerty CL, Peipert JF, Weitzen S, Hendrix SL, Holley RL, Nelson DB, et al. Predictors of chronic pelvic pain in an urban population of women with symptoms and signs of pelvic inflammatory disease. Sex Transm Dis 2005;32:293-299.

75. Wolner-Hanssen. Diagnosis of pelvic inflammatory disease. In DV Landers and RL Sweet, eds. Pelvic inflammatory disease. Spring-Verlang, New York 60-75.

76. Walker CK, Kahn JG, Washington AE, Peterson HB, Sweet RL. Pelvic inflammatory disease: metaanalysis of antimicrobial regimen efficacy. J Infect Dis 1993;168:969-78.

77. Dunbar-Jacob J, Sereika SM, Foley SM, Bass DC, Ness RB. Adherence to oral therapies in pelvic inflammatory disease. J Women's Health 2004;13:285-291.

78. Rustomjee R, Kharsany AB, Connolly CA, Karim SS. A randomized controlled trial of azithromycin versus doxycycline/ciprofloxacin for the syndromic management of sexually transmitted infections in a resource-poor setting. J of Antimicrobial Chemotherapy 2002;49:875-78.

79. Malhotra M, Sharma JB, Batra S, Arora R, Sharma S. Ciprofloxacin-tinidazole combination, fluconazole-azithromicin-secinidazole-kit and doxycycline-metornidazole combination therapy in syndromic management of pelvic inflammatory disease: a prospective randomized controlled trial. Ind J Med Sci 2003;57:549-55.

80. Bevan CD, Ridgway GL, Rothermel CD. Efficacy and safety of azithromycin as monotherapy or combined with metronidazole compared with two standard multidrug regimens for the treatment of acute pelvic inflammatory disease. J Int Med Res 2003;31:45-54.

81. Hemsel DL, Ledger WJ, Martens M, Osborne NG, Thomason JL. Concerns regarding the Centers for Disease Control's published guidelines for pelvic inflammatory diseae. CID 2001;32:103-107.

82. Walker CK, Workowski KA, Washington AE, Soper D, Sweet RL. Anaerobes in pelvic inflammatory disease: implications for the Centers for Disease Control and Preventions' guidelines for treatment of sexually transmitted diseases. Clin Infect Dis 1999;28:529-36.

83. Kosseim M. Ronald A. Plummer FA. D'Costa L. Brunham RC. Treatment of acute pelvic inflammatory disease in the ambulatory setting: trial of cefoxitin and doxycycline versus ampicillin-sulbactam. Antimicrobial Agents Chem 1991;35(8):1651-6.

84. Brunham RC, MacLean IW, Binns B, Peeling RW. Chlamydia trachomatis: Its role in tubal infertility. J Infect Dis 1985;152(6):1275-82.

85. Teisala K, Heinonen PK, Asine R. Second laparoscopy after treatment of acute pelvic inflammatory disease. Obstet Gynecol 1987;69:343.

86. Heinonen PK, Leinone M. Fecundity and morbidity following acute pelvic inflammatory disease treated with doxycycline and metronidazole. Arch Gynecol Obstet 2003;268:284-288.

87. McCormick WM, Mowroozi K, Alpert S, Sackel SG, Lee YH, Lowe Ew, et al. Acute pelvic inflammatory disease: characteristics of patients with gonoccal and nongonoccal infection and evaluation of their response to treatment with aqueous procaine penicillin G and spectinomycin hydrocholoride. Sex Transm Dis 1977;4:125-31.

88. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. Pain 1992;50:133-49.

89. Matthews KA, Katholi CR, McCreath H, et al. Blood Pressure Reactivity to Psychological Stress Predicts Hypertension in the CARDIA Study. Circulation 2004; 110:74-78.

90. Hughers GH, Cutter G, Donahue R, Friedman GD, Hulley S, et al. Recruitment in the coronary artery disease risk development in young adults (CARDIA) study. Cont Clin Trials 1987;8:68S-73S.

91. Friedman GD, Cutter G, Donahue R, Hughes GH, Hulley SB, et al. CARDIA: study design, recruitment and some characteristics of the examined subjects. J Clin Epidemiol 1988;11:1105-1116.

92. Zhang S, Folsom AR, Flack JM, Liu K. Body fat distribution before pregnancy and gestational diabetes: findings from coronary artery risk development in young adults (CARDIA) study. BMJ;1995:1139-1140.

93. Wilcox AJ, Horney LF. Accuracy of spontaneous abortion recall. Am J Epidemiol 1984;120:727-733.

94. Joffe M Zhimin L. Male and female factors in fertility. Am J Epidemiol 1994;140(10):921-929.