HELDA
HELSINGIN YLIOPISTO
HELSINGFORS UNIVERSITET
UNIVERSITY OF HELSINKI

UNIVERSITY OF HELSINKI

https://helda.helsinki.fi

Reproductive system infections in women : upper genital tract, fetal, neonatal and infant syndromes

Brunham, Robert C.

2020-07

Brunham , R C & Paavonen , J 2020 , ' Reproductive system infections in women : upper genital tract, fetal, neonatal and infant syndromes ' , Pathogens and disease , vol. 78 , no. 5 , 023 . https://doi.org/10.1093/femspd/ftaa023

http://hdl.handle.net/10138/332077
https://doi.org/10.1093/femspd/ftaa023

acceptedVersion

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.

Reproductive System Infections in Women: Upper Genital Tract, Fetal, Neonatal and Infant Syndromes

Robert C Brunham, MD

Department of Medicine, University of British Columbia,

Vancouver, Canada

and

Jorma Paavonen, MD PhD

Department of Obstetrics and Gynecology, University of Helsinki,

Helsinki, Finland

Corresponding author:

Dr. Robert C Brunham, MD

655 West 12th Ave., Vancouver, B.C., V5Z 4R4

Tel: 604-707-2405; Fax: 604-707-2401

Email: Robert.Brunham@bccdc.ca

Keywords: Reproductive System Infections, Women's health, Neonatal and Infant Health, Sexually Transmitted Diseases

Uncorrected Proof

Downloaded from https://academic.oup.com/femspd/advance-article-abstract/doi/10.1093/femspd/ftaa023/5848195 by Hulib user on 08 June 2020

Abstract

Lower genital tract infection or blood borne spread of infection are the two principal modes for infection of the upper genital tract or for infection of the fetus, neonate or infant. *Treponema pallidum* or human immunodeficiency virus are the two most common blood borne pathogens that infect the fetus, neonate or infant. Most infections of the upper genital tract however spread along epithelia surfaces from the vagina or cervix to the upper genital tract or chorioamnion, fetus, neonate or infant. These infections are caused by either pathogens associasted with a dysbiotic vaginal microbiome or which are sexually transmitted. The clinical syndromes that these pathogens produce in the lower genital tract were discussed in part one of this review. We now discuss the syndomes and pathogens that affect the upper genital tract of both non-pregnant and pregnant women.

Introduction

The reproductive system perspective is most helpful in understanding the variety of infectious disease syndromes which occur in the upper genital tract of non-pregnant and pregnant women despite the fact that the specific pathogens are the same. We now review those upper genital tract syndromes.

Endometrium, Fallopian Tube and Ovaries

Ascending infection from the vagina or cervix cause most cases of acute and subclinical pelvic inflammatory disease. Pelvic inflammatory disease is the major cause of tubal infertility and ectopic pregnancy and may be a risk factor for ovarian cancer.

Uncorrected Proof

Downloaded from https://academic.oup.com/femspd/advance-article-abstract/doi/10.1093/femspd/ftaa023/5848195 by Huiib user on 08 June 2020

Pelvic Inflammatory Disease, Tubal Infertility and Ectopic Pregnancy

Pelvic inflammatory disease can spontaneously ascend from vaginal and cervical infection or follow therapeutic abortion or childbirth. Pelvic inflammatory disease can be classified as acute (< 30 days duration), subclinical or chronic [1]. Acute pelvic inflammatory disease is defined as complaints of lower abdominal pain together with findings of pelvic organ tenderness, on bimanual examination and with signs of lower genital tract inflammation such as endocervical mucopus and/or excess neutrophils (outnumbering squamous epithelial cells) in microscopic examination of vaginal fluid. Sexually transmitted cervical pathogens such as *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Mycoplasma genitalium*[2] which are important causes of mucopurulent cervicitis are major causes of acute and subclinical pelvic inflammatory disease. Organisms associated with bacterial vaginosis and desquamative inflammatory vaginitis as part of dysbiotic vaginal microbiomes are also important causes of pelvic inflammatory disease. Both vaginal and cervical pathogens spread contiguously from the lower genital tract to the endometrium and fallopian tubes where they cause plasma cell endometritis[3, 4]. Bacterial vaginosis organisms as they spread into the upper genital tract also produce a dense biofilm on the endometrial epithelial surface[5].

Acute pelvic inflammatory disease clinically responds to a variety of antimicrobial agents[6] and recommended treatments for pelvic inflammatory disease have been standardized by several public health organizations including the Centres for Disease Control and Prevention in the United States. Systematic meta analysis of recommended antimicrobial regimens show that no regimen is superior in terms of clinical and microbiologic responses[7]. However long-term reproductive disability remains distressingly high following treatment of pelvic inflammatory disease with 15% or more of women suffering from recurrent pelvic inflammatory disease or tubal infertility[1]. No antimicrobial regimen has been demonstrated to be superior in reducing the risk of post infection sequelae. The reasons for the dismal outcomes are complex and likely include irreversible inflammatory and immune mediated

Uncorrected Proof

Downloaded from https://academic.oup.com/femspd/advance-article-abstract/doi/10.1093/femspd/ftaa023/5848195 by Hulib user on 08 June 2020

damage to the delicate structures of the fallopian tube prior to therapy. Future trials of antimicrobial therapies for pelvic inflammatory disease need to include long-term evaluation of determinants of post pelvic inflammatory disease sequelae such recurrent pelvic inflammatory disease, tubal infertility and ectopic pregnancy. One study that used this type of design noted that polymicrobial tubal infection with abscess formation or *Chlamydia trachomatis* pelvic inflammatory disease had significantly worse fertility outcome than women with gonococcal pelvic inflammatory disease[8]. In large seroepidermiologic studies rates of pregnancy were significantly lower and pelvic inflammatory disease recurrence rates were significantly higher among women with high titers of *Chlamydia trachomatis* antibodies than those without such antibodies among a cohort of women treated for pelvic inflammatory disease suggesting that *Chlamydia trachomatis* pelvic inflammatory disease carries a worse fertility prognosis than other causes of pelvic inflammatory disease[9].

Since *Chlamydia trachomatis* is such an important cause of pelvic inflammatory disease and sequelae it has been studied in considerable detail from epidemiologic, genomic and immunological points of view. Epidemiological analysis suggests that both duration of infection and reinfection are important in *Chlamydia trachomatis* pelvic inflammatory disease pathogenesis[10-12]. Immunoepidemiologic studies suggest that antibodies to *Chlamydia trachomatis* molecular components such as *Chlamydia trachomatis* heat shock protein 60 correlate with sequelae such as tubal infertility, ectopic pregnancy, pelvic inflammatory disease and perihepatitis perhaps as a marker of long duration infection[13-18]. It is unlikely that *Chlamydia trachomatis* heat shock protein 60 is directly involved in disease pathogenesis[9]. Rather antibody responses to *Chlamydia trachomatis* heat shock protein 60 are co-linear with antibody to the whole *Chlamydia trachomatis* bacterial cell. Heat shock protein 60 is a single molecule measure of immune responses to persistent *Chlamydia trachomatis* infection because of its immunodominance during long duration infection[19]. In aggregate immunoepidemiological studies of *Chlamydia trachomatis* heat shock protein 60 show that antibody dominant immune responses correlate with diseases such as pelvic inflammatory disease and its sequelae.

Uncorrected Proof

Downloaded from https://academic.oup.com/femspd/advance-article-abstract/doi/10.1093/femspd/ftaa023/5848195 by Hulib user on 08 June 2020

Dominant interferon gamma or IL-10 cellular immune responses to *Chlamydia trachomatis* heat shock protein 60 correlate with protection to infection or susceptibility to immunopathology[20, 21]. Since humoral and cellular immune responses to heat shock protein 60 are reciprocally related it is possible that genetic factors that regulate Th1 versus Th2 immune responses determine *Chlamydia trachomatis* immunobiology.

Both ectopic pregnancy and tubal infertility are seroepidemiologically linked to prior *Chlamydia trachomatis* pelvic inflammatory disease. Most cases involve subclinical pelvic inflammatory disease. Histopathologically the fallopian tube of women with *Chlamydia trachomatis* associated ectopic pregnancy is characterized by plasma cell infiltration without evidence of ongoing infection[13-15]. In Africa where tubal infertility is especially common prior *Chlamydia. trachomatis* and *Neiserria gonorrhoeae* pelvic inflammatory disease are serologically linked with tubal infertility and predominantly occurs among women who previously gave birth[22]. In these settings *Chlamydia trachomatis* and *Neiserria gonorrhoeae* infections are common and public health control programs for maternal care are often not in place. As a consequence parturition is a major cause of ascending *Chlamydia trachomatis* and *Neissera gonorrhoeae* infection resulting in post partum endometritis, pelvic inflammatory disease and secondary infertility[23, 24]. Ophthalmia neonatorum is the major marker for mothers at risk of post partum pelvic inflammatory disease[25]. Screening and treatment for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in pregnancy substantially reduces the risk of post partum pelvic inflammatory disease and ophthalmia neonatorum.

Ovarian cancer

Pelvic inflammatory disease may be a risk factor for ovarian cancer. Inflammation has been suggested as a causal link between pelvic inflammatory disease and ovarian cancer[26, 27]. Seroepidemiologic studies have linked prior *Chlamydia trachomatis* infection with ovarian cancer although the association has been inconsistent[28-30]. Nonetheless given that *Chlamydia trachomatis* produces

Uncorrected Proof

Downloaded from https://academic.oup.com/femspd/advance-article-abstract/doi/10.1093/femspd/ftaa023/5848195 by Hulib user on 08 June 2020

double strand DNA breaks in infected host cells a casual pathway may exist where *Chlamydia trachomatis* infection of fallopian tube epithelial cells acts as a co-factor together with other inflammatory oncogenic factors in the genesis of ovarian cancer[31].

Chorioamnion, Fetus, Neonate and Infant

Reproductive system infections during pregnancy rarely result in pelvic inflammatory disease. Rather ascending infection most commonly infects the chorioamnion and fetus or transmits during birth to cause disease in the neonate or infant. The major diseases produced by infection are chorioamnionitis and prematurity, stillbirth and neonatal and infant infection.

Chorioamnionitis and Prematurity

Chorioamnionitis is pathologically defined as inflammation of the fetal membranes and is the single most important risk factor for preterm birth and can be subclinical or clinical in presentation[32]. Chorioamnionitis is also the major risk factor for neonatal sepsis and death[33]. Organisms associated with bacterial vaginosis (*Gardnerella vaginalis, Mobiluncus* sp., *Bacteroides* sp. etc) and the vaginal dysbiosis associated with desquamative inflammatory vaginitis (group B Streptococci, *Escherichia coli* etc) are commonly isolated from fetal membranes when chorioamnionitis is found pathologically[34]. Treatment during later months of pregnancy for bacterial vaginosis does not prevent preterm birth whereas treatment during early pregnancy may do so[35]. Intrapartum antimicrobial treatment for group B Streptococci reduces the risk of neonatal sepsis due to this microbe. Intrapartum gonococcal infection is also a major cause of pre term birth in areas where untreated maternal gonorrhea is common[36].

Uncorrected Proof

Downloaded from https://academic.oup.com/femspd/advance-article-abstract/doi/10.1093/femspd/ftaa023/5848195 by Hulib user on 08 June 2020

Stillbirth

Intrauterine fetal death can result from maternal reproductive system infection. Blood borne spread of human immunodeficiency virus or syphilis to the placenta and fetus are the major microbial causes of stillbirth in Africa[37].

Neonatal Infection

Maternal infection with *Chlamydia trachomatis* or *Neisseria gonorrhoeae* frequently results in ophthalmia neonatorum[36, 38]. Thirty to 40% of neonates exposed to *Chlamydia trachomatis* or *Neisseria gonorrhoeae* intrapartum become infected postpartum[39]. Neonates with gonococcal ophthalmia neonatorum can be successfully treated with antimicrobials including ceftriaxone[40, 41]. Ocular prophylaxis dramatically reduces the incidence of gonococcal and chlamydial ophthalmia neonatorum[42]. Neonates exposed during birth to maternal *Chlamydia trachomatis* infection are also at increased risk of developing infant pneumonia[43]. All these risks for neonatal and infant infectious disease can be prevented by maternal screening for reproductive system infections during and prior to pregnancy.

Conclusions

Viewing reproductive system infections in women as encompassing diseases of the vulva, vagina, cervix, endometrium, fallopian tubes and ovaries and the chorioamnion, fetus, neonate and infant shows how they share common epidemiology, microbial etiologies and pathogenic mechanisms. The syndrome, etiologic agent, treatment and prevention modalities are summarized in table 1.

Existing disease control programs based on screening and treatment remain effective and important in improving the reproductive health of women. The impact of the absence of reproductive health services is seen in epidemiological settings where sexually transmitted infections are common and untreated. In such settings

Uncorrected Proof

Downloaded from https://academic.oup.com/femspd/advance-article-abstract/doi/10.1093/femspd/ftaa023/5848195 by Huiib user on 08 June 2020

tubal factor infertility is tragically common, maternal syphilis or human immunodeficiency virus infection increase stillbirth rates 3 to 5 fold and 3 to 5 % of newborns develop gonococcal or chlamydial ophthalmia neonatorum. In particular screening and treatment for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, syphilis and human immunodeficiency virus substantially improves the reproductive health of women as well as reduces the risk of fetal, neonatal and infant disease. Ocular prophylaxis at birth prevents ophthalmia neonatorum. Rolling out and supporting these programs at a global level is a major goal for global health programs best done within a comprehensive reproductive system framework.

An important realization has been that control programs for the bacterial sexually transmitted pathogens profoundly alter the clinical features and patterns of disease. Because of the extended duration of time post infection that it takes to acquire immunity to these pathogens, shortening the duration of infection by screening and antimicrobial treatment reduces herd immunity and shifts the clinical features of infection towards subclinical infection. Thus disease control programs based on screening and antimicrobial treatment have important limits. The major sexually transmitted bacterial pathogens *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Treponema pallidum* will require vaccines to fully achieve control. Fortunately molecular study of these pathogens has generated promising candidates that can soon be brought forward for clinical evaluation as was successfully done for human papilloma virus. Vaccines are at the forefront of research to prevent reproductive system infections of women.

Despite advancements in understanding reproductive system infections in women much remains incompletely known. For instance the causes of vulvar vestibulitis need to be understood at a microbial and immunological level because it is such a common cause of painful intercourse. An understanding of the cause of recurrent vulvovaginal candidiasis may well improve prevention of vulvar vestibulitis. Why a Lactobacilli dominant microbiome is lost in some women resulting in susceptibility to bacterial vaginosis , trichomoniasis and desquamative inflammatory vaginitis needs to be understood. Diagnostic test development is needed to improve control of reproductive system infection in women. In particular

Uncorrected Proof

Downloaded from https://academic.oup.com/femspd/advance-article-abstract/doi/10.1093/femspd/ftaa023/5848195 by Huiib user on 08 June 2020

molecular tests for the microbial composition of the vaginal microbiome would improve the recognition of bacterial vaginosis, desquamative inflammatory vaginitis, trichomoniasis and candidiasis. Additionally improved imaging modalities of the uterus, fallopian tubes and ovaries would advance diagnosis of clinical and subclinical pelvic inflammatory disease and its sequelae. Current evidence suggests that magnetic resonance imaging has the resolution necessary to image the pelvis including the fallopian tubes and should be used in future studies of pelvic inflammatory disease[44, 45]. Lastly tests that diagnose subclinical chorioamnionitis have the potential to have a major impact on preterm birth[46, 47].

Recurrent infection remains a major problem for reproductive system infection in women. Randomized clinical trials using antimicrobials, sex steroids and immune modulators for vulvar vestibulitis, bacterial vaginosis, desquamative inflammatory vaginitis, vulvovaginal candidiasis and pelvic inflammatory disease may lead to therapies which reduce relapse rates and/or post disease sequelae. Strategies that stabilize a Lactobacilli vaginal microbiome may prevent recurrences of bacterial vaginosis, desquamative inflammatory vaginitis and protect against a broad variety of sexually transmitted pathogens. Strategies that enhance the proportion of male sexual partners who are treated will be particularly important to reducing recurrence rates for the sexually transmitted pathogens.

Additional antimicrobial interventions in pregnancy are needed to address the continuing problem of prematurity. It is remarkable that despite the continuing im provement in survival of neonates born prematurely the rates of prematurity have not changed. The impact of treatment of vaginal dysbiosis in pregnancy on preterm birth remains incompletely defined. Treatment of bacterial vaginosis in late pregnancy does not prevent preterm birth however treatment in early pregnancy may do so[35]. Studies should focus on early interventions, use of probiotics with antimicrobials and evaluate effects on both preterm birth and histopathologic evidence of chorioamnionitis. Given the propensity of bacterial vaginosis to produce endometrial biofilm formation, evaluation of treatment prior to pregnancy may even be useful.

Uncorrected Proof

Downloaded from https://academic.oup.com/femspd/advance-article-abstract/doi/10.1093/femspd/ftaa023/5848195 by Hulib user on 08 June 2020

Two Nobel Prizes in Medicine and Physiology have been awarded to scientists for advances they have made in women's reproductive health. In 2008, Nobel Prizes were awarded to Harald zur Hausen for the discovery of human papilloma viruses causing cervical cancer and to Francoise Barre-Sinoussi and Luc Montagnier for their discovery of the human immunodeficiency virus. In 2010 the Nobel Prize was given to Robert Edwards for the development of human in vitro fertilization therapy initially used in the treatment of post pelvic inflammatory disease tubal infertility. Despite the awarding of Nobel Prizes, this class of infectious diseases remains under-studied, under-appreciated, under-diagnosed and inconsistently treated. Future research which addresses the major questions are likely to improve the reproductive health of women and the population health of humanity[48].

Uncorrected Proof

Downloaded from https://academic.oup.com/femspd/advance-article-abstract/doi/10.1093/femspd/ftaa023/5848195 by Hulib user on 08 June 2020

Table 1: Reproductive system infection syndromes in women and their recommended treatment and prevention.

Syndrome	Etiology	Treatment	Prevention
Genital ulcer disease	*Treponema pallidum*	Penicillin	
	Haemophilus ducreyi	Ceftriaxone	
	Klebsiella granulomatis	Azithromycin	
	Chlamydia trachomatis (Lymphogranuloma venerum)	Doxycycline	
	Herpes simplex virus	Acyclovir	
Genital warts	Human papilloma virus	Topical Podofilox	HPV vaccine
Vulvar vestibulitis	Cutaneous hypersensitivity to microbial antigens	Surgery	
Vulvovaginitis	*Candida albicans*	Fluconazole	
Bacterial vaginosis	*Gardnerella vaginalis*	Topical clindamycin	
	Atopobium		
	Mobiluncus		
	Other anaerobes		
Desquamative inflammatory vaginitis	Group B Streptococci	Topical clindamycin	
	E. coli		
	Staph aureus		
	Other facultative anaerobes		
Trichomoniasis	*Trichomonas vaginalis*	Metronidazole	
Mucopurulent cervicitis	*Chlamydia trachomatis*	Azithromycin	
	Neisseria gonorrhoeae	Ceftriaxone plus Azithromycin	
	Mycoplasma genitalium	Moxifloxacin	
	Herpes simplex virus	Acyclovir	
Cervical neoplasia	Human papilloma virus	Surgery	HPV vaccine, Pap smears

Uncorrected Proof

Downloaded from https://academic.oup.com/femspd/advance-article-abstract/doi/10.1093/femspd/ftaa023/5848195 by Hulib user on 08 June 2020

Table 1 Continue

Syndrome	Etiology	Treatment	Prevention
Pelvic inflammatory disease	*Chlamydia trachomatis* *Neisseria gonorrhoeae* *Mycoplasma genitalium* *Peptostreptococci* *Prevotella* *Sheathia* Other anaerobes β-*Streptococci* *E. coli* *Haemophilus influenza* *Staph aureus*	Ceftriaxone plus Azithromycin plus Metronidazole	Condom Screening and treatment for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*
Tubal infertility	*Chlamydia trachomatis* *Neisseria gonorrhoeae* *Mycoplasma genitalium* Polymicrobial abscess	in vitro fertilization	Screening and treatment for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*
Ectopic pregnancy	*Chlamydia trachomatis* *Neisseria gonorrhoeae*	Methotrexate or surgery	Screening and treatment for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*
Ovarian cancer	Post pelvic inflammatory disease	Surgery Chemotherapy Immunotherapy	
Prematurity	Subclinical Chorioamnionitis		Screening and treating bacterial vaginosis in early pregnancy
Clinical amnionitis	Group B Streptococci *E. coli* *Prevotella* Bacteroides *Neisseria gonorrhoeae* *Chlamydia trachomatis*	Cefoxitin plus doxycycline	
Stillbirth	*Treponema pallidum* Human immunodeficiency virus	Penicillin Antiretroviral therapy	Screening and treatment for syphilis and HIV in pregnancy

Uncorrected Proof

Downloaded from https://academic.oup.com/femspd/advance-article-abstract/doi/10.1093/femspd/ftaa023/5848195 by Hulib user on 08 June 2020

Table 1 Continue

Syndrome	Etiology	Treatment	Prevention
Congenital or Perinatal infection	*Treponema pallidum*	Penicillin	Screening and treatment for syphilis and HIV in pregnancy
	Human immunodeficiency virus	Antiretroviral therapy	
	Herpes simplex virus	Acyclovir	
Neontal sepsis	Group B Streptococci *E. coli*	Cefotaxime	
Ophthalmia Neonatum	*Chlamydia trachomatis*	Erythromycin	Ocular prophylaxis Erythromycin
	Neisseria gonorrhoeae	Ceftriaxone	
Laryngeal Papillomatosis	Human papilloma virus	Surgery	HPV vaccine
Infant pneumonia	*Chlamydia trachomatis*	Erythromycin	Screening and treatment for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*

Uncorrected Proof

Downloaded from https://academic.oup.com/femspd/advance-article-abstract/doi/10.1093/femspd/ftaa023/5848195 by Hulib user on 08 June 2020

References :

1. Brunham RC, Gottlieb SL, Paavonen J. Pelvic inflammatory disease. *The New England journal of medicine* 2015; **372**(21): 2039-48.
2. Cohen CR, Manhart LE, Bukusi EA, et al. Association between Mycoplasma genitalium and acute endometritis. *Lancet* 2002; **359**(9308): 765-6.
3. Paavonen J, Kiviat N, Brunham RC, et al. Prevalence and manifestations of endometritis among women with cervicitis. *American journal of obstetrics and gynecology* 1985; **152**(3): 280-6.
4. Eckert LO, Hawes SE, Wolner-Hanssen PK, et al. Endometritis: the clinical-pathologic syndrome. *American journal of obstetrics and gynecology* 2002; **186**(4): 690-5.
5. Swidsinski A, Verstraelen H, Loening-Baucke V, Swidsinski S, Mendling W, Halwani Z. Presence of a polymicrobial endometrial biofilm in patients with bacterial vaginosis. *PloS one* 2013; **8**(1): e53997.
6. Brunham RC. Therapy for acute pelvic inflammatory disease: a critique of recent treatment trials. *American journal of obstetrics and gynecology* 1984; **148**(3): 235-40.
7. Savaris RF, Fuhrich DG, Duarte RV, Franik S, Ross JDC. Antibiotic therapy for pelvic inflammatory disease: an abridged version of a Cochrane systematic review and meta-analysis of randomised controlled trials. *Sexually transmitted infections* 2018.
8. Brunham RC, Binns B, Guijon F, et al. Etiology and outcome of acute pelvic inflammatory disease. *The Journal of infectious diseases* 1988; **158**(3): 510-7.
9. Ness RB, Soper DE, Richter HE, et al. Chlamydia antibodies, chlamydia heat shock protein, and adverse sequelae after pelvic inflammatory disease: the PID Evaluation and Clinical Health (PEACH) Study. *Sexually transmitted diseases* 2008; **35**(2): 129-35.
10. Brunham RC, Rekart ML. Considerations on Chlamydia trachomatis disease expression. *FEMS immunology and medical microbiology* 2009; **55**(2): 162-6.
11. Cohen CR, Brunham RC. Pathogenesis of Chlamydia induced pelvic inflammatory disease. *Sexually transmitted infections* 1999; **75**(1): 21-4.
12. Rekart ML, Gilbert M, Meza R, et al. Chlamydia public health programs and the epidemiology of pelvic inflammatory disease and ectopic pregnancy. *The Journal of infectious diseases* 2013; **207**(1): 30-8.
13. Brunham RC, Maclean IW, Binns B, Peeling RW. Chlamydia trachomatis: its role in tubal infertility. *The Journal of infectious diseases* 1985; **152**(6): 1275-82.
14. Brunham RC, Binns B, McDowell J, Paraskevas M. Chlamydia trachomatis infection in women with ectopic pregnancy. *Obstetrics and gynecology* 1986; **67**(5): 722-6.
15. Brunham RC, Peeling R, Maclean I, Kosseim ML, Paraskevas M. Chlamydia trachomatis-associated ectopic pregnancy: serologic and histologic correlates. *The Journal of infectious diseases* 1992; **165**(6): 1076-81.

Uncorrected Proof

Downloaded from https://academic.oup.com/femspd/advance-article-abstract/doi/10.1093/femspd/ftaa023/5848195 by Hulib user on 08 June 2020

16. Peeling RW, Kimani J, Plummer F, et al. Antibody to chlamydial hsp60 predicts an increased risk for chlamydial pelvic inflammatory disease. *The Journal of infectious diseases* 1997; **175**(5): 1153-8.
17. Eckert LO, Hawes SE, Wolner-Hanssen P, et al. Prevalence and correlates of antibody to chlamydial heat shock protein in women attending sexually transmitted disease clinics and women with confirmed pelvic inflammatory disease. *The Journal of infectious diseases* 1997; **175**(6): 1453-8.
18. Money DM, Hawes SE, Eschenbach DA, et al. Antibodies to the chlamydial 60 kd heat-shock protein are associated with laparoscopically confirmed perihepatitis. *American journal of obstetrics and gynecology* 1997; **176**(4): 870-7.
19. Brunham RC. Perspective: my 37 year journey through Chlamydia research: Chlamydia antigen analysis using monoclonal antibodies and major histocompatibility complex molecules. *Pathogens and disease* 2017; **75**(8).
20. Cohen CR, Koochesfahani KM, Meier AS, et al. Immunoepidemiologic profile of Chlamydia trachomatis infection: importance of heat-shock protein 60 and interferon- gamma. *The Journal of infectious diseases* 2005; **192**(4): 591-9.
21. Kinnunen A, Surcel HM, Halttunen M, et al. Chlamydia trachomatis heat shock protein-60 induced interferon-gamma and interleukin-10 production in infertile women. *Clinical and experimental immunology* 2003; **131**(2): 299-303.
22. Cates W, Farley TM, Rowe PJ. Worldwide patterns of infertility: is Africa different? *Lancet* 1985; **2**(8455): 596-8.
23. Temmerman M, Laga M, Ndinya-Achola JO, et al. Microbial aetiology and diagnostic criteria of postpartum endometritis in Nairobi, Kenya. *Genitourinary medicine* 1988; **64**(3): 172-5.
24. Plummer FA, Laga M, Brunham RC, et al. Postpartum upper genital tract infections in Nairobi, Kenya: epidemiology, etiology, and risk factors. *The Journal of infectious diseases* 1987; **156**(1): 92-8.
25. Fransen L, Nsanze H, D'Costa LJ, Brunham RC, Piot P. Parents of infants with ophthalmia neonatorum: a high-risk group for sexually transmitted diseases. *Sexually transmitted diseases* 1985; **12**(3): 150-4.
26. Stewart LM, Spilsbury K, Jordan S, et al. Risk of high-grade serous ovarian cancer associated with pelvic inflammatory disease, parity and breast cancer. *Cancer epidemiology* 2018; **55**: 110-6.
27. Rasmussen CB, Kjaer SK, Albieri V, et al. Pelvic Inflammatory Disease and the Risk of Ovarian Cancer and Borderline Ovarian Tumors: A Pooled Analysis of 13 Case-Control Studies. *American journal of epidemiology* 2017; **185**(1): 8-20.
28. Ness RB, Goodman MT, Shen C, Brunham RC. Serologic evidence of past infection with Chlamydia trachomatis, in relation to ovarian cancer. *The Journal of infectious diseases* 2003; **187**(7): 1147-52.
29. Ness RB, Shen C, Bass D, et al. Chlamydia trachomatis serology in women with and without ovarian cancer. *Infectious diseases in obstetrics and gynecology* 2008; **2008**: 219672.
30. Fortner RT, Terry KL, Bender N, et al. Sexually transmitted infections and risk of epithelial ovarian cancer: results from the Nurses' Health Studies. *British journal of cancer* 2019.

Uncorrected Proof

Downloaded from https://academic.oup.com/femspd/advance-article-abstract/doi/10.1093/femspd/ftaa023/5848195 by Huib user on 08 June 2020

31. Mi Y, Gurumurthy RK, Zadora PK, Meyer TF, Chumduri C. Chlamydia trachomatis Inhibits Homologous Recombination Repair of DNA Breaks by Interfering with PP2A Signaling. *mBio* 2018; **9**(6).
32. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. *The New England journal of medicine* 2000; **342**(20): 1500-7.
33. Brunham R, Holmes K, Eschenbach D. Sexually transmitted diseases in pregnancy. New York: McGraw-Hill, Inc.; 1984.
34. Hillier SL, Martius J, Krohn M, Kiviat N, Holmes KK, Eschenbach DA. A case-control study of chorioamnionic infection and histologic chorioamnionitis in prematurity. *The New England journal of medicine* 1988; **319**(15): 972-8.
35. Paavonen J, Brunham R. Bacterial vaginosis and desquamative inflammatory vaginitis. *NEJM* 2018; **379**(23): 2246-54.
36. Elliott B, Brunham RC, Laga M, et al. Maternal gonococcal infection as a preventable risk factor for low birth weight. *The Journal of infectious diseases* 1990; **161**(3): 531-6.
37. Temmerman M, Plummer FA, Mirza NB, et al. Infection with HIV as a risk factor for adverse obstetrical outcome. *Aids* 1990; **4**(11): 1087-93.
38. Fransen L, Nsanze H, Klauss V, et al. Ophthalmia neonatorum in Nairobi, Kenya: the roles of Neisseria gonorrhoeae and Chlamydia trachomatis. *The Journal of infectious diseases* 1986; **153**(5): 862-9.
39. Laga M, Plummer FA, Nzanze H, et al. Epidemiology of ophthalmia neonatorum in Kenya. *Lancet* 1986; **2**(8516): 1145-9.
40. Fransen L, Nsanze H, D'Costa L, Brunham RC, Ronald AR, Piot P. Single-dose kanamycin therapy of gonococcal ophthalmia neonatorum. *Lancet* 1984; **2**(8414): 1234-7.
41. Laga M, Naamara W, Brunham RC, et al. Single-dose therapy of gonococcal ophthalmia neonatorum with ceftriaxone. *The New England journal of medicine* 1986; **315**(22): 1382-5.
42. Laga M, Plummer FA, Piot P, et al. Prophylaxis of gonococcal and chlamydial ophthalmia neonatorum. A comparison of silver nitrate and tetracycline. *The New England journal of medicine* 1988; **318**(11): 653-7.
43. Datta P, Laga M, Plummer FA, et al. Infection and disease after perinatal exposure to Chlamydia trachomatis in Nairobi, Kenya. *The Journal of infectious diseases* 1988; **158**(3): 524-8.
44. Tukeva TA, Aronen HJ, Karjalainen PT, Molander P, Paavonen T, Paavonen J. MR imaging in pelvic inflammatory disease: comparison with laparoscopy and US. *Radiology* 1999; **210**(1): 209-16.
45. Molander P, Sjoberg J, Paavonen J, Cacciatore B. Transvaginal power Doppler findings in laparoscopically proven acute pelvic inflammatory disease. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 2001; **17**(3): 233-8.
46. Myntti T, Rahkonen L, Tikkanen M, Paavonen J, Stefanovic V. Vaginally obtained amniotic fluid samples in the diagnosis of subclinical chorioamnionitis. *Acta obstetricia et gynecologica Scandinavica* 2016; **95**(2): 233-7.
47. Myntti T, Rahkonen L, Patari-Sampo A, et al. Comparison of amniotic fluid matrix metalloproteinase-8 and cathelicidin in the diagnosis of intra-amniotic

Uncorrected Proof

Downloaded from https://academic.oup.com/femspd/advance-article-abstract/doi/10.1093/femspd/ftaa023/5848195 by Hulib user on 08 June 2020

infection. *Journal of perinatology : official journal of the California Perinatal Association* 2016; **36**(12): 1049-54.
48. Meza R, Pourbohloul B, Brunham RC. Birth cohort patterns suggest that infant survival predicts adult mortality rates. *Journal of developmental origins of health and disease* 2010; **1**(3): 174-83.

Uncorrected Proof

Downloaded from https://academic.oup.com/femspd/advance-article-abstract/doi/10.1093/femspd/ftaa023/5848195 by Hulib user on 08 June 2020