Sexually transmitted diseases and infertility

Danielle G. Tsevat, BA; Harold C. Wiesenfeld, MD, CM; Caitlin Parks, MD; Jeffrey F. Peipert, MD, PhD

Female infertility, including tubal factor infertility, is a major public health concern worldwide. Most cases of tubal factor infertility are attributable to untreated sexually transmitted diseases that ascend along the reproductive tract and are capable of causing tubal inflammation, damage, and scarring. Evidence has consistently demonstrated the effects of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* as pathogenic bacteria involved in reproductive tract morbidities including tubal factor infertility and pelvic inflammatory disease. There is limited evidence in the medical literature that other sexually transmitted organisms, including *Mycoplasma genitalium*, *Trichomonas vaginalis*, and other microorganisms within the vaginal microbiome, may be important factors involved in the pathology of infertility. Further investigation into the vaginal microbiome and other potential pathogens is necessary to identify preventable causes of tubal factor infertility. Improved clinical screening and prevention of ascending infection may provide a solution to the persistent burden of infertility.

Key words: chlamydia, gonorrhea, infertility, STD, STI

Overview

Infertility, which is defined as the inability to conceive after ≥12 months of regular unprotected sexual intercourse, is a common public health concern worldwide. Globally, 9% of reproductive-aged women, including nearly 1.5 million women in the United States, are infertile.[1,2] The burden of infertility is inordinately higher among women in developing countries; in some regions of south and central Asia, sub-Saharan and northern Africa, the Middle East, and eastern Europe, infertility rates can reach up to 30% in reproductive-aged women.[3] The inability to conceive not only creates a considerable cost burden for patients and the health care system but is also a major psychological stressor for millions of couples.[4] In many areas of the world, especially in low- and middle-income countries where having biological children is highly valued and expected of couples, involuntary infertility can lead to stigmatization, economic deprivation, social isolation and loss of status, public shame and humiliation, and in some cases, violence.[5,6] Female infertility may be attributed to a number of factors, typically divided into endocrine, vaginal, cervical, uterine, tubal, and pelvic-peritoneal factors, and although estimates vary, approximately 15-30% of cases still remain unexplained.[7] Further insight into the causes of infertility is necessary to help alleviate this multifactorial burden on society.

Tubal factor infertility (TFI) ranks among the most common causes of infertility, accounting for 30% of female infertility in the United States, and is even more prevalent in certain communities.[8] Paralleling the aforementioned global infertility disparity, TFI is disproportionately common in women in developing countries; for example, it has been shown to account for >85% of female infertility cases in regions of sub-Saharan Africa, compared to 33% of cases worldwide.[3] Most cases of TFI are due to salpingitis, an inflammation of the epithelial surfaces of the fallopian tubes, and subsequent pelvic-peritoneal adhesions, both of which are most commonly caused by previous or persistent infections.[9,10] Bacteria ascend along mucosal surfaces from the cervix to the endometrium and ultimately to the fallopian tubes. This causal pathway presents itself clinically as acute pelvic inflammatory disease (PID), which in turn is strongly associated with subsequent TFI. In fact, approximately 15% of women with PID develop TFI, and the number of episodes of PID a woman experiences is directly proportional to her risk of infertility.[11,12] However, the majority of women with TFI do not have a history of clinically diagnosed acute PID, but rather develop asymptomatic or minimally symptomatic salpingitis as a result of upper genital tract infection.[9,13] Examining the effect of those infections, particularly those that occur in the absence of clinically evident PID, is critical to understanding TFI.

Several sexually transmitted diseases (STDs), including *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, have been widely studied to understand their role in salpingitis and infertility. Additionally, several other pathogens such as *Mycoplasma genitalium*, *Trichomonas vaginalis*, and other microorganisms within the vaginal microbiome, may also play roles in tubal damage and other potential causes of infertility. Still, data suggest that not all infections yield the same long-term sequelae. The roles of different STD

From the Division of Clinical Research, Department of Obstetrics and Gynecology, Washington University in St Louis School of Medicine, St Louis, MO (Ms Tsevat and Dr Parks); Division of Gynecologic Specialties, Department of Obstetrics and Gynecology, University of Pittsburgh School of Medicine, Pittsburgh, PA (Dr Wiesenfeld); and Department of Obstetrics and Gynecology, Indiana University School of Medicine, Indianapolis, IN (Dr Peipert).

Received May 27, 2016; revised July 29, 2016; accepted Aug. 8, 2016.

Drs. Wiesenfeld and Peipert contributed to this manuscript on behalf of the Infectious Disease Society for Obstetrics & Gynecology (IDSOG), and the Publications Committee of IDSOG has approved the final version.

Disclosure: Dr Peipert receives research support from Bayer, Merck, and Teva, and serves on advisory boards for Teva and Perrigo. The other authors report no financial conflicts of interest in the past 12 months.

Corresponding author: Jeffrey F. Peipert, MD, PhD. jpeipert@iu.edu

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2016.08.008

pathogens, co-infections, and interactions with host characteristics, including their individual vaginal microbiome, may all affect a woman's subsequent ability to conceive. While screening and treatment efforts for *C trachomatis* and *N gonorrhoeae* have been developed to reduce the incidence of PID and subsequent TFI, additional data are needed to determine the role of other potential pathogens and whether early detection can prevent tubal damage. In this article, we discuss the pathogens *C trachomatis*, *N gonorrhoeae*, *Mycoplasma genitalium*, *T vaginalis*, and other potential organisms that may affect female fertility, and we address the clinical importance of screening and preventing the spread of those infections.

Methodology

We conducted a comprehensive literature search to identify articles by using the electronic databases MEDLINE, Embase, Web of Science, and CINAHL, in addition to scrutinizing references of identified articles. Within each database, we combined the term "female infertility" with 4 different infection terms: "*Chlamydia trachomatis*," "*Neisseria gonorrhoeae*," "*Mycoplasma genitalium*," and "*Trichomonas vaginalis*." Within the MEDLINE database, we refined the search by excluding the Medical Subject Headings unrelated to female infertility and at least 1 of the 4 organisms. Within the Embase search, we used Emtree to identify terms, and used both "female infertility" and "uterine tube occlusion" as focused search terms to combine with each infection. We filtered results to only include articles published in English between 1975 and April 2016. Additional relevant articles were identified from bibliographies and by the recommendation of medical experts. The inclusion of the articles used in the analysis was based on quality of the study and relevance to this review: studies were excluded if they were conducted with few participants, had no comparison group, or constituted case reports. Studies that did not report sufficient data to determine the association with female infertility or reproductive morbidities were excluded for lack of relevance to the topic of review.

C trachomatis and *N gonorrhoeae*

C trachomatis and *N gonorrhoeae* have been extensively shown to be associated with infertility, particularly by causing tubal inflammation. In fact, early speculation regarding the effect of *N gonorrhoeae* on female fertility dates back to the 1870s, when the German-born gynecologist Emil Noeggerath published his revolutionary claims about gonorrhea as a clinical condition in his book *Latent Gonorrhoea Especially with Regard to its Influence on Fertility in Women*.[14] Although he may have widely overestimated its repercussions (postulating that gonorrhea causes 90% of female infertility), his theories eventually sparked the initiation of further investigations.[15] When the bacterium *N gonorrhoeae* was finally isolated, Noeggerath's controversial claims regarding the persistence of this "venereal poison" in the reproductive organs and its pathologic consequences were reexamined.[16] Studies conducted more than a century later have since demonstrated the impact of *C trachomatis* and *N gonorrhoeae* on subsequent infertility.

C trachomatis, the most common reportable disease in the United States, affects nearly 1.5 million people in the US annually.[17] Unfortunately, however, because *C trachomatis* infections are asymptomatic in most women,[18,19] infections are often unnoticed, untreated, and underreported. For almost 40 years, evidence has shown that untreated ascending *C trachomatis* infection can lead to irrevocable damage in the fallopian tubes including proximal and distal tubal occlusions leading to infertility.[9] The increased amount of heat shock protein synthesized by *C trachomatis* induces a proinflammatory immune response in the human fallopian tube epithelia, resulting in scarring and tubal occlusion.[9,20,21] A number of seroepidemiological studies have examined the prevalence of antibodies to *C trachomatis* and chlamydial heat shock protein in women with laparoscopically or hysterosalpingographically confirmed fallopian tube damage and ectopic pregnancies.[22-28] The results of these studies indicate that history of *C trachomatis* infection is associated with a significantly increased risk of tubal infertility in women, regardless of the infection invoking clinical symptoms.[20,25,29-32] Extensive research has also shown that *C trachomatis* infection can cause PID, which often precedes infertility. Today, *C trachomatis* accounts for approximately 50% of cases of acute PID in developed countries.[33] Among PID patients, those with prior *C trachomatis* infection have been shown to be more likely to experience subsequent infertility than those without a history of *C trachomatis* infection.[32-35]

While *C trachomatis* seropositivity has long been shown to influence fallopian tube patency,[36] the use of a newer, more sensitive and specific antichlamydial assay by Geisler and coworkers[37] has only recently been shown to hold promise as a measure of tubal function.[38] In a cohort study of 1250 infertile women with documented tubal patency undergoing fertility treatment, *C trachomatis* seropositivity using the antibody subclasses IgG1 and IgG3 was tested.[39] Results showed that of these 2 antibody subclasses tested, seropositivity to *C trachomatis* based on IgG3 detection was a strong predictor of both failure to conceive and ectopic pregnancy outcomes. Because IgG3 has been shown to be involved in early inflammatory response to infection,[40] the detection of IgG3 in these women may reflect a recently cleared or persistent *C trachomatis* infection, contributing to fallopian tube damage while perhaps not yet leading to blockage of the fallopian tubes.[39]

In another study of subfertile women with no visible tubal pathology, positive chlamydial antibody testing was associated with a 33% lower spontaneous pregnancy rate than those without chlamydial antibodies.[28,39] Coppus and colleagues[28] suggest that these low pregnancy rates may not only be caused by the known mechanism of chronic inflammatory response causing fallopian tube damage; persistent *C trachomatis* infections have also been shown to elicit an autoimmune response to human heat shock proteins, which may elevate the risk for impaired embryo development