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PERSPECTIVE

Does Active Oral Sex Contribute to Female Infertility?

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(See the major article by Carlson et al, on pages 990–9.)

Based on recent, historical, and circumstantial evidence, we present a multifactorial hypothesis that has potential direct implications on the epidemiology and management of chlamydial infection and disease in humans. We propose that (1) like its veterinary relatives, the oculogenital pathogen *Chlamydia trachomatis* evolved as a commensal organism of the human gastrointestinal (GI) tract primarily transmissible via the fecal-oral route; (2) in the modern era, *C. trachomatis* causes "opportunistic" infection at non-GI sites under conditions driven by improved sanitation/hygiene and reduced fecal-oral transmission; and (3) the rise in the practice of oral sex is contributing to the increased prevalence of *C. trachomatis* in the human GI tract. Infectious organisms produced in the GI tract and reaching the rectum may then chronically contaminate and infect the female urogenital tract, thereby potentially contributing to the most serious sequelae of chlamydial infection in women: pelvic inflammatory disease, ectopic pregnancy, and tubal factor infertility.

Keywords. oral sex; *Chlamydia trachomatis*; commensalism; fecal-oral transmission; female infertility.

We hypothesize that:

1. All members of the Chlamydiaceae have evolved primarily as commensals of the digestive tract of their host(s) with fecal-oral transmission (FOT) as the principal route of dissemination to new hosts. In communities where FOT is reduced, the occurrence of chlamydiae in the digestive tract is reduced.
2. *Chlamydia trachomatis*, a commensal microorganism of the human gastrointestinal tract (GIT), is an opportunistic pathogen in the genital and respiratory tracts and the conjunctiva. Under conditions of reduced FOT, direct contact is the primary mode of transmission.
3. *Chlamydia trachomatis* is efficiently transmitted to the GIT of new hosts via oral sex. The increasing practice of oral sex is contributing to the increased prevalence of *C. trachomatis* in the human GIT in communities where FOT was previously reduced.

Tenets 1–2 imply a paradigm shift in the study of *C. trachomatis* infection reflecting its revised status from principal pathogen to commensal organism causing opportunistic infection at mucosal epithelia other than its evolutionarily preferred gastrointestinal (GI) site. For instance, the ability of these organisms to vary antigenically [1], the odd structures and properties of chlamydial peptidoglycan [2] and lipo-oligosaccharide [3, 4], and the extrusion of plasma membrane–bound inclusions or inclusion fragments [5] may have evolved to facilitate chlamydial survival and colonization of the GIT.

Tenet 3 implies that orally inoculated chlamydiae that survive in and colonize the GIT may reach the rectum and, chronically or episodically, contaminate and/or infect the female genital tract, eventually progressing to cause or contribute to tubal pathology. The global hypothesis therefore raises the question: Does active oral sex contribute to female infertility?

ALL *CHLAMYDIA* SPECIES HAVE EVOLVED TO COLONIZE THE GIT

An indirect but compelling argument that supports the idea that *C. trachomatis* colonizes the GIT without clinical disease is that most, if not all, other *Chlamydia* species are first and foremost innocuous gut commensals. This was previously suggested [6–8], and Supplementary Data 1 briefly documents supportive evidence for each species. Infectious chlamydiae that colonize the digestive tract of animals may be disseminated to new hosts via FOT, and may behave as opportunistic pathogens when contaminating a non-GI site in the same host or another susceptible host of the same species. Alternatively, FOT may occur to a different animal species or zoonotically to humans (eg, psittacosis). Confirmed or suspected colonization of the digestive tract of their host by veterinary *Chlamydia* species therefore begs the question: Is *C. trachomatis* also an innocuous, unsuspected commensal colonizer of the human GIT? If so, can it also be transmitted via FOT? Are ingested chlamydiae

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able to survive host defenses and reach the rectum? From there, can they contaminate and infect the female genital tract?

CHLAMYDIA TRACHOMATIS CAUSES OPPORTUNISTIC INFECTIONS AT GENITAL, OCULAR, AND RESPIRATORY MUCOSAL EPITHELIA

The proposed revision of *C. trachomatis*' status as a gut commensal organism complements but does not challenge the well-documented evidence of *C. trachomatis* infections at urogenital, ocular, and respiratory sites and transmission via sexual activity or direct contact. Opportunity for feces-borne transmission of veterinary chlamydiae to non-enteric sites abounds in natural and domestic environments and is facilitated by the ability of chlamydial elementary bodies to remain infectious for some time outside their hosts. In addition, dissemination from the GIT to distant sites may also occur via circulating infected cells such as macrophages or dendritic cells, thus allowing access to different sites in the host. In humans, such mechanisms are proposed to contribute to the dissemination of *Chlamydia pneumoniae* from infected lungs to atherosclerotic plaques [9, 10] and of *C. trachomatis* from the infected genital tract to synovial cells and synovial membrane of arthritic joints [11, 12]. Conversely, infectious chlamydiae may target the GIT from distant sites by similar mechanisms as suggested by recent experiments using the mouse/*Chlamydia muridarum* model system [13]. In humans, in addition to oral inoculation, infectious chlamydiae may also occur at the rectum via genital-rectal autoinoculation or via rectal intercourse with an infected partner. Overall, this suggests that infectious chlamydiae have multiple ways to access the GIT, from where they have ample, nonmutually exclusive opportunities to access non-GI sites from endogenous or environmental feces-contaminated sources and via circulating monocytic cells of the immune system.

MODERN SANITATION AND ENHANCED PERSONAL HYGIENE HAVE CURTAILED TRANSMISSION OF *C. TRACHOMATIS* VIA THE FECAL ORAL ROUTE

Modern sanitation consists of an array of measures aimed at globally eliminating or minimizing contact between humans and waste from humans and animals. Enteric bacteria including *Escherichia coli* pathotypes (eg, *E. coli* O157:H7) [14] and environmental microorganisms such as *Vibrio cholerae* [15] may be harmless in animal hosts but are capable of causing severe disease in humans. Global sanitation measures that have historically reduced FOT of enteric pathogens to humans, together with enhanced personal hygiene [16], have dramatically altered the composition and diversity of the human gut microbiota. We propose that, in the pre–sexual revolution/human immunodeficiency virus (HIV)/AIDS pandemic period, when oral sex was not as commonly practiced as it is today, this included a significant reduction of commensal *C. trachomatis* from the gut microbiota in humans. In support of this hypothesis, we review historical and epidemiological evidence (Supplementary Data 2) that suggests the existence of a missing reservoir of infectious chlamydiae for trachoma, the other notorious disease caused by *C. trachomatis*, in regions of the world that have poor to no sanitation.

ACTIVE ORAL SEX "REINTRODUCES" *C. TRACHOMATIS* IN THE GIT

Seventy five percent of women report they have ever engaged in oral sex [17]. The popular belief that oral sex is "not sex" [18] and the search for safer sex in the face of the HIV epidemic have fueled the notion that oral sex is relatively safe and does not require physical protection such as a condom or dam. Indirect evidence [19–21] suggests that oral sex is a frequent recreational activity of young sexually active high-school or college-age adolescents/young adults who think that the risk-to-benefit ratio of oral sex is relatively small. Reality is different: although the probability of transmitting HIV via oral sex is lower than via vaginal or anal sex, the practice is still associated with many diverse risks [22]. Oral sex is known to transmit a variety of viral and bacterial sexually transmitted infections, including herpes, syphilis, gonorrhea, human papillomavirus (HPV), and hepatitis A/B infection [23, 24], and the association with HPV-related oropharyngeal cancer is a growing concern [25].

Orally inoculated *C. trachomatis* colonizing the GIT of its host may, however, systematically elude detection through a combination of factors. No reason a priori exists for an apparently healthy woman or her physician to suspect oral or rectal chlamydia when a nucleic acid amplification diagnostic test from a cervical swab is negative. Oral, rectal, or fecal samples are not routinely tested for *C. trachomatis*. Perhaps most importantly, orally acquired chlamydiae may elude the unsuspecting woman's own immune system as it fails to recognize or respond to a microbe that is quietly colonizing the GIT.

We hypothesize that infectious chlamydiae are transmitted to the female genital tract via active oral sex and colonization of unidentified GIT site(s). We further hypothesize that all *Chlamydia* species have evolved conserved mechanisms to evade innate and immune host defenses in the GIT, and that orally inoculated chlamydiae will contaminate and infect not only the rectum but also the lower genital tract in women. GIT colonization may allow the organism to "persist" undetected by the human host and tolerated by the immune system for extended periods of time. Evidence from murine models of chlamydial genital infection strongly supports this hypothesis (Supplementary Data 3). Repeated, unsuspected exposure of the reproductive tract to even low levels of infectious chlamydiae may cause chronic inflammation, low-level infection, and/or disturbance of the vaginal microbiota that, individually or together, may facilitate ascending infection to the upper genital tract. The outcome is that, having made the relatively short, final journey

from the rectum to the vagina and cervix, orally acquired chlamydia may contribute to chronic chlamydial infection of the female reproductive tract and its most serious sequelae: pelvic inflammatory disease, tubal factor infertility, and life-threatening ectopic pregnancies.

Conclusions

The proposed relationship between oral sex, GIT colonization, repeated exposure/infection of the female lower genital tract, ascending infection, tubal disease, and its sequelae raises many more questions that can be listed here, some of which may be testable experimentally. For instance, if sanitation facilitated the establishment of *C. trachomatis* as a sexually transmitted pathogen, then the reverse should be true in areas where FOT is still ever-present, eg, cholera-endemic areas. If oral sex is significantly contributing to the inoculation of *C. trachomatis* into the GIT, where along the 9-m length does colonization occur? In developed, sanitized regions of the world, sexual transmission remains the major route by which *C. trachomatis* disseminates among men and women. GIT colonization may, however, be making a comeback with the help of increasing oral sex practices. A sobering thought is that with oral sex and GIT colonization, *C. trachomatis* may have "evolved" yet another, most unsophisticated way to elude the clinician, the infected patient, and the patient's own immune system.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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