Reproductive Tract Infections and Infertility

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MHR lecture Notes

OVERVIEW

- Infectious agents can impair various important human functions, including reproduction.
- Bacteria, fungi, viruses and parasites are able to interfere with the reproductive function in both sexes.
- Infections of male genito-urinary tract account for about 15% of the case of male infertility.
- These infections can affect different sites of the male reproductive tract and spermatozoa themselves

- In female, microorganisms are certainly involved in cervical, tubal, and peritoneal damage,
- Tubo-peritoneal damage seems to be the foremost manner in which microorganisms interfere with human fertility.

OVERVIEW

- Reproductive tract infections (RTIs) include three types of infection:
  - Sexually transmitted diseases (STDs), such as chlamydia, gonorrhea, chancroid, and human immunodeficiency virus (HIV);
  - Endogenous infections, which are caused by overgrowth of organisms normally present in the genital tract of healthy women, such as bacterial vaginosis or vulvovaginal candidiasis;
  - Iatrogenic infections, which are associated with improperly performed medical procedures such as unsafe abortion or poor delivery practices *(1). RTIs are preventable, and many are treatable as well.*

OVERVIEW

- "Infertility can be defined as the lack of a conception after at least one year of constant, unprotected vaginal sexual intercourse, in the absence of known reproductive pathology"

  NICE guideline, CG156

- The underlying causes may be ascribed to pathologic conditions affecting one or both members of a couple

OVERVIEW

- Intracellular
- Energy parasites
- Elementary body
- Reticulate body
- Inclusion bodies – HP, LCL
- Biotypes/ serotypes
- Tissue culture
- *C. trachomatis*
- Trachoma
- Inclusion conjunctivitis
- Lymphogranuloma venereum
- Frei test
- Genital chlamydiasis
- *C. psittaci*
- Psittacosis
- Ornithosis
- *C. pneumoniae*

Infertility and RTIs

- There is a complex relationship between infections and infertility.
- Many microorganisms seem to be involved in male reproductive failure in various ways, and to different degrees of statistical association.
- Infections of male lower genital tract seem to have little importance, if not, of an occlusion.
- Infections involving other parts of the male GUT, may cause a microbial colonization of the semen.

Infertility and RTIs……

- Virtually all parts of the female reproductive system may be influenced by infectious agents
- Vaginal infections and cases of endometritis, leading to uterine sinechiae, are less common than tubal occlusions resulting from salpingitis.
- Adhesions, caused by PID, seem to affect the functional status of the tubes more harshly than that of the uterus.

Bacteria: *Genital mycoplasmas*

Mycoplasmas:

- These microorganisms are frequently present in the genital tract and semen of both fertile and infertile men
- particularly true for *Ureaplasma urealyticum*, and slightly for both *Mycoplasma hominis* and *Mycoplasma genitalium*.
- Ureaplasmas are a cause of nonchlamydial, non-gonococcal urethritis (NGU) in men.

Mycoplasmas

- Overnight co-incubation with *M. hominis* can produce small but statistically significant differences in motility, morphology, and fertilization potential in human spermatozoa.
- *U. urealyticum* is associated with the production of ROS, even in absence of leucocytospermia.
- *M. genitalium* can attach to human spermatozoa, and thus could be carried out by motile sperm, causing female genital diseases and infertility.

Mycoplasmas

- In female, *M. genitalium* is strongly associated with cervicitis, endometritis and serologically with salpingitis-PID complex, and may account for a number of cases of infertility .
- Antibodies against this pathogen were found in patients with tubal factor infertility (TFI), even in cases where the presence of Chlamydia trachomatis was excluded.
- Diagnosed by isolation , DNA Probe, PCR

Neissseria gonorrhoeae

- This bacterium is known to cause urethritis
- Its incidence in the western world has diminished over the last two decades, as a result of more accurate sexual hygiene following the onset (HIVAIDS) epidemic.
- Gonococcal infections in women are believed to be in decline with encouraging evidence even from Africa.
- The primary gonococcal infection is present in the endocervix, with concomitant urethral infection.

- Ascending infection may occur in 10–20% of infected women and can result in acute PID that may manifest as salpingitis, endometritis, tubo-ovarian abscess, all of which can lead to scarring, ectopic pregnancy, sterility, and chronic pelvic pain

Neissseria gonorrhoeae….

- N. *gonorrhoeae incubated with tubal epithelial cell produced IL-1*α, IL-β and TNF-α suggested the genesis of gonoccus-induced infertility.
- Diagnosis is by Gram smear of urethral discharge (male) or EC specimen in symptomatic female; GNC in pairs associated with PMNs
- supported by immunological or molecular procedures.

Chlamydia trachomatis

- *C. trachomatis* has a worldwide distribution, affecting both sexes but has a much greater impact on females than on males.
- It particularly affects young women and sexually active adolescents
- Serovar D–K causes NGU, epididymitis, prostatitis, cervicitis, urethritis, endometritis, salpingitis, and perihepatitis in women.
- Induces Reiter's syndrome, proctitis, and conjunctivitis in both sex

Chlamydia trachomatis….

- *C. trachomatis* – **2 biovars**: TRIC & LGV

1. **TRIC** – Trachoma, Inclusion conjunctivitis
   - divided into 12 serovars

2. **LGV** – Lymphogranuloma venereum – 3 serovars

Human diseases

Species	Serotype	Disease
C. trachomatis	A, B, Ba, C	Endemic blinding trachoma
C. trachomatis	D to K	Inclusion conjunctivitis. Genital chlamydiasis
C. trachomatis	L1, L2, L3	Lymphogranuloma venereum
C. psittaci	Many serotypes	Psittacosis
C. pneumoniae		Acute resp. disease

C. trachomatis....

- C. trachomatis, when co-incubated with human spermatozoa in vitro, seems to impair sperm motility, and cause premature death, perhaps as an effect of the chlamydial lipopolysaccaride
- Infection by C. trachomatis is related to the production of anti-sperm antibodies (ASA), but the extent to which ASAs actually affect fertility is yet to be clarified
- There is a clear relationship between male infection, which is often asymptomatic and the possibility of transmission to the more susceptible female partner

C. trachomatis….

- In female, infections interfere seriously with human reproduction.
- Cause of tubal obstructions, lacerations and ectopic pregnancy, and can result in PID, adnexitis, local or diffuse peritonitis, and formation of adhesions.
- C. trachomatis is believed to be one of the major causes of cervical factor infertility (CFI), as a result of the alterations of the epithelium and mucus composition, and by the presence of inflammatory cells

C. trachomatis....

- The chlamydial 10 kDa and 57 kDa HSP (cHSP10 and cHSP57/60, respectively) show an amazing analogy to human proteins.
- Thus, there formation of antibodies against the HSP60 in the serum and follicular fluid of women which have negative impact on embryonal growth, and increase risk of adverse pregnancy outcomes
- antibodies against HSP60 and positive for *C. trachomatis* seem to have a greater probability of tubal scaring and ectopic pregnancy, compared to women only seropositive.

C. trachomatis….

- There also seems to be a cross-reactivity btw HSP10 and an embryonic protein, the early pregnancy factor (EPF), and this may cause abortions.
- cHSP10 too, probably correlate to the severity of the disease in females and with the presence TFI. (La verda et al, 2008)
- HSP57/60 also has been found to induce trophoblast apoptosis by stimulating the TLR4, which naturally mediates immune responses in placenta. (Equilis et al, 2006)

C. trachomatis….

- Genetic conditions may have an important role in the whole process of C. trachomatis-induced damage.
- Some variants of the gene that controls IL-10 production may be involved in the impairment of the immune response against the bacterium
- Although there is no absolute "gold standard" for chlamydia tests, NA amplification (PCR, LCR, TMP) assays show sensitivity ≥90% compared with 60–70% for culture and 60% for antigen assays.

Enterobacteriaceae

- E. coli is the most common cause of nonsexually transmitted epididymo-orchitis and is involved in about 80% of total acute or chronic prostatitis.
- *E. coli* may, therefore, be implicated in the genesis of infertility, and the same might be true for other enterobacteria belonging to the genera *Klebsiella, Salmonella* and *Proteus.*
- *Ps. aeruginosa* can cause epididymitis and prostatitis, and may, in this manner, interfere with male fertility. (Weidner et al, 1999)

Gram-positive cocci

- Streptococci and Staphylococci normally colonize the male urethra, whilst Enterococci seem to be more frequently present in the seminal tract.
- All these genera seem to be implicated in the genesis of prostatitis and epididymitis, and thus may impair male fertility.
- Enterococci are often present in the semen of infertile men, and their presence is associated with impaired seminal parameters

Gram-positive cocci….

- Streptococci and Staphylococci too are often present in the urethra of infertile men, but unlike Enterococci, do not seem to impair semen quality .

- Mehta et al. mention an association between the presence of Enterococcus, oligospermia and teratospermia. (Mehta et al,2002)

Gardnerella vaginalis

- *G. vaginalis* seems to be very common in the genital tract of men with suspected infertility, and is also frequent among infertile men and even more among their wives

- Common agent associated with bacterial vaginosis, apart from *M. hominis* and *U. urealyticum*, *Mobiluncus spp.*, *Bacteroides spp.* and *peptostreptococcus spp.* Are also common
- Ascending dissemination of the involved species may lead to tubal factor infertility

Helicobacter pylori

- *H. pylori* may be the only microorganism to impair fertility without infecting the genital tract or its glandular structures.
- *H. pylori* was significantly more prevalent among infertile men and women than among healthy controls
- Antibodies against *H. pylori* were found in genital fluids of infertile patients (100% of follicular fluids, 50% of sperm samples, a minority of vaginal secretions)
- Anti-helicobacter Atb cross-react with the tails and the pericentriolar area of human spermatozoa. ??

Yeasts

- *Candida albicans* commonly colonizes the urethra, but rarely the accessory glands.
- C. albicans, as well as its filtrates, have an inhibitory effect on human sperm motility, and impaired the ultrastructure of human spermatozoa, which could be associated with male infertility
- C. albicans is a common commensal of the female genital tract and rarely cause condition more serious than recurrent vulvovaginal andidiasis (RVVC) in females.

Parasites and other rare conditions

- Trichomonas vaginalis has a worldwide distribution and it affects both sexes
- In males, it is a rare cause a NGU and perhaps prostatitis
- Proteinases released by T. vaginalis can also inhibit sperm motility *in vitro*, even after the microorganism has been removed from the culture medium
- The parasite is frequently present within infertile couples, particularly among women.

T. vaginalis

- The clear association btw the presence of T. vaginalis and bacterial vaginosis
- Trichomoniasis is assoc with mild vaginal and cervical damage, and doesnt seem capable of producing CFI.
- *T. vaginalis* is assoc decreased C3 and C4 complement factors, increased IgA level in vaginal discharge, and increased serum prolactin.
- This protozoan disease has also been associated with adverse pregnancy outcomes

T. vaginalis….

- T. vaginalis promotes the action of *M. hominis*, by transporting the bacterium inside the protozoa cell.

- This offers protection from the action of the immune system and the effects of therapies, and favors its spread through the genital tract,

- Other protozoarian diseases have been associated with impaired fertility
- Genital amoebiasis can seriously damage female reproductive system and cause sterility.
- Toxoplasmosis may give infertility by producing ASA, or by causing hypogonadotropic hypogonadism.
- Genital tuberculosis, leprosy, and helminthes (eg Filarisis) may damage the testes and impair male fertility.

Viruses

- HSV infection of the male genital tract is implicated with male infertility, as it is associated with decreased semen quality
- The presence of HSV DNA in human spermatozoa has been proven
- Antiviral treatment of male infertility patients positive for HSV in semen resulted in successful pregnancies
- HSV infections, on the other hand, seem to have no significant association with cervical factor infertility

Human papilloma viruses (HPV)

- HPV were found in testicular biopsies of azoospermic men.
- when present inside sperm cells, they may be related to impaired sperm motility and asthenozoospermia.
- Fernandez et al. found, in 1998, an association between HPV and infertility, particularly TFI

Human Immunodeficiency Viruses (HIV)

- HIV may impair semen parameters by itself and certainly deteriorates the outcome of concomitant genital infections
- HIV has a negative impact also on female fertility, but it is not clear to what extent this is due: to the activity of the virus itself, or to other concomitant genital infections, or even to drug side effects

Summary

Agents	Men	Women	Diagnoses
Neisseria gonorrhoeae	Urethritis, epididymitis, orchitis, infertility, proctitis, pharyngitis, disseminated gonococcal infection	Cervicitis, endometritis, salpingitis, pelvic inflammatory disease, infertility, preterm rupture of membranes, perihepatitis, proctitis, pharyngitis, disseminated gonococcal infection	Isolation pathogen, detection of antigen or nucleic acid, DFA, EIA
Chlamydia trachomatis	Urethritis, epididymitis, orchitis, infertility, proctitis, pharyngitis, Reiter's syndrome; LGV: ulcer, inguinal swelling, proctitis	Cervicitis, endometritis, salpingitis, pelvic inflammatory disease, infertility, preterm rupture of membranes, perihepatitis, proctitis, pharyngitis, Reiter's syndrome; LGV: ulcer, inguinal swelling, proctitis	Isolation pathogen (tissue culture), direct detection of antigen (DFA, fluorescent tagged monoclonal antibodies), nucleic acid amplification (PCR), EIA
Treponema pallidum	Primary ulcer with local adenopathy, skin rashes, condylomata lata; bone, cardiovascular and neurological damage	Primary ulcer with local adenopathy, skin rashes, condylomata lata; bone, cardiovascular and neurological damage; abortion, premature delivery	Dark-field microscopy, PCR, FTA, EIA, FTA-ABS
Mycoplasma genitalium	Urethral discharge (NGU)	Bacterial vaginosis; probably PID, cervicitis, endometritis	Cultural methods, PCR, IFA
Ureaplasma urealyticum	Urethral discharge (NGU)	Bacterial vaginosis; probably PID	Cultural methods, PCR, IFA
Mycoplasma hominis		Vaginitis, cervicitis, postpartum sepsi	Cultural methods, PCR, IFA
Gardnerella vaginalis		Vaginosis (works synergically with anaerobic bacteria: Bacteroides, Peptococcus)	Dense aggregates of Gram-negative bacilli on desquamated epithelial cells (clue cells); cultural methods
HSV-2, HSV-1 (less commonly)	Anogenital vesicular lesions and ulcerations	Anogenital vesicular lesions and ulcerations	Tissue culture, DFA, PCR, EIA, direct DNA detection
HPV	Penile and anal warts; carcinoma of the penis	Vulval, anal and cervical warts, cervical carcinoma, vulval carcinoma, anal carcinoma	Pap smear, DNA hybridization, PCR
Trichomonas vaginalis	NGU, often asymptomatic	Vaginosis, frothy yellow vaginal discharge, preterm birth, low birth weight babies	Wet mount microscopy, demonstration of nucleic acid
Candida albicans	Superficial infection of the glans penis	Vulvovaginitis with thick curd-like discharge, vulval itching or burning	Cultural methods, REA, PFGE, PCR


Thanks

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