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Reproductive Tract Infection : A Scourge for Women's Health

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Summary

In India, because of gender discrimination although women are more vulnerable to RTIs they have less opportunity for early diagnosis and treatment. Ignorance, illiteracy and myths along with exposure to media and clubs have accelerated the rate of spread of these infections in adolescents in urban and rural areas.

In this the efforts of various FOGSI committees towards sex education in adolescents and conducting reproductive health workshops at district and primary health centre level need to be strengthened.

Ongoing oncogene research in HPV if confirmed in extended epidemiological studies would provide a genetic marker to identify women at risk for developing cervical cancer for closer monitoring and timely intervention.

Introduction

Reproductive tract infections (RTIs) have become widespread today because of the changing social fabric and unconventional sexual behaviour. The incidence of RTIs is now reaching enormous proportions globally; for Sexually Transmitted Diseases (STDs), according to WHO, the estimated figures of four major STDs in women, in the reproductive age group are 12.2 million for syphilis, 167.2 million for Trichomoniasis, 62.2 million for Gonorrhoea and 89.1 million for Chlamydial infection (Gerbase, 1998). STDs facilitate HIV infection. In a recent rural study in India, the incidence of HIV in the high-risk group was 17.5% of which 4.7% presented as recurrent leucorrhoea (Redkar & Redkar, 1999).

There has been a conceptual shift in women's health program from Family Planning in 1950's to Mother and Child Health (MCH) to Family Welfare in 1960's to Safe Motherhood in 1980's, and with an alarming increase of RTIs in India now the emphasis is on Comprehensive Health Care which also includes management of RTIs in the 1990s.

RTIs compromise women's health much more than that of men; women have less say in the use of protective methods of contraception and sexual relations. Often asymptomatic lower RTIs spread easily to the pelvis and abdomen during procedures like abortion or delivery, MTPs, IUD insertions and diagnostic or therapeutic curetage (D&C). Some of these interventional procedures for diagnosis or treatment in Gynaecology can also inadvertently lead to ascending infections e.g. intrauterine inseminations, hysterosalpingography. Poor general health of women due to malnutrition and/or anaemia can predispose to RTIs.

International Women's Health Coalition (IWHC)

categorizes RTIs into i) STDs including HIV infection ii) Endogenous with overgrowth of facultative microorganisms iii) Iatrogenic infections acquired during medical procedures (Germain A, et al, 1992). Though RTIs include all these categories, the present review will mainly focus on the first category.

RTIs – A Scourge for Women's Health

RTIs have an adverse impact on women's health from acute life-threatening emergencies e.g. ectopic pregnancy to chronic debility due to chronic pelvic pain to serious long-term sequelae like cervical cancer. They also have social implications due to infertility and impact on the future progeny. Some of the adverse impacts of RTIs are shown in Table 1. Rampant RTIs have raised the incidence of sequelae: infertility 41%, chronic pelvic pain 43%, recurrent episodes of Pelvic Inflammatory Disease (PID) 24%, and ectopic pregnancy 2.4%. Recurrent episodes of PID lead to almost doubling of the percentage of infertility (Gerbase, 1998, Germaine 1992).

Table I:

Adverse Impact of RTIs on Women's Health
Chronic vaginal discharge
Chronic backache
Pelvic inflammatory disease
Infertility/Subfertility
Ectopic pregnancy
Postpartum sepsis and postabortal sepsis
Foetal wastage: spontaneous abortions
LBW: prematurity and/or IUGR
Congenital/perinatal infections
Warts/ulcers
Carcinoma cervix

Even though the decades-long association of RTIs and cancer cervix was well known, definitive evidence has emerged recently. The relative risk of cervical cancer in women co-infected with Human Papilloma Virus (HPV) and Herpes Simplex Virus II (HSV) is twice that of the women infected with only HPV. Other organisms like Trichomonas vaginalis, Anaerobic bacteria, Chlamydia trachomatis, and HIV have also been shown to be associated with precancerous conditions and cervical carcinogenesis (Ellerbrock et al 2000, Joshi JV, 1993). The mechanisms of RTI-induced carcinogenesis are being elucidated by recent techniques in molecular biology. The development of cervical carcinoma correlates more closely with certain types of HPV infections viz. HPV 16 and 18. These HPV types encode for major oncoproteins E6 and E7. The E6 protein binds to the cellular tumour-suppressor protein P53. HPV-associated tumours revealed overrepresentation of a type of arginine 72 P53 allele as compared to the normal population. The frequency of HPV induced cervical cancer is seven times more in women with P53 gene polymorphisms with arginine instead of proline, indicating a genetic predisposition to cervical cancer (Storey, 1998).

Efforts by eminent leaders of cytology with training programmes for Pap smears, colposcopy and population screening have helped significantly in the downstaging of cervical cancer at primary levels of health care screening by visual inspection of cervix and examination with acetic acid also helps this goal (Sankaranarayan, 1999). Screening for gene polymorphism, if confirmed by larger studies in different ethnic groups, may identify women at high risk but may not be practical for the masses.

Sexually Transmitted Diseases: A Humongous Global Problem

There are 333 million new cases of STDs annually. According to WHO's estimate a total of 150 million (45.6%) occurred in the South East Asia region (Gerbase, 1998). Such a humongous problem of STDs is due to a change in sexual behaviour as well as due to the urban migration of men, who visit sexual workers.

In India too, the problem of STDs has increased tremendously. The prevalence of STDs from some of the centres in India is shown in Table II.

HIV: The HIV epidemic has reached catastrophic proportion in less than a decade. Relative risk (R.R.) of acquiring HIV in presence of STDs has increased; R.R. is 4.7 for Genitourinarydisease/Chancroid, 1.2-2.2 for Syphilis, 3.5 for Herpes simplex II, 3.5 for Gonorrhoea, 3.2 for Chalmydia trachomatis, and 2.7 for Trichomonas (Germain, 1992). Currently, an estimated 30.6 million adults and children have HIV / AIDS. In India, according to the reports provided by National AIDS Control Organization (NACO) a total of 67,311 persons have been reported as HIV positive, number of AIDS cases are 5002. A recent report (UNAIDS) suggests that India has the greatest number of people infected with HIV-more than 4 millions. Close to 1% of total HIV seropositive are antenatal mothers and 4% of AIDS cases are children and 44% are adolescents (15-19 yr.).

TableII: Prevalence of Genital Infections: Indian Studies

Authors	Population	Methods	Prevalence (%)*
Bang et al 1989	Village community	Wet smear Microscopy Culture	CA-34, BV-62, TV-14, TP-11, NG-0.3
Joshi et al 1993	Commercial sex workers (CSW)	PAP smear Serology ELISA (Antigen)	CT-26, HPV-16
Joshi et al 1996	Family welfare clinics	PAP smear Culture Serology	TV-3, CA-4, BV-21, HSV-0.7, HPV-3, CT 18, NG 0.4, HIV-0
Mahadani et al 1998	Patients with leucorrhoea	PAP smears Gram smears	TV-17, CA-10, BV-4, NG-0.6
Palayekar et al 2000	Family welfare Clinics	Cytology Fluorescent antibody, Geimsa, Pap smear	CT-16.8%

TV-Trichomonas vaginalis, CA-Candida albicans, BV-Bacterial vaginosis, TP-Treponema pallidum, NG-Neisserria gonorrhoea, CT-Chlamydia trachomatis, HSV-Herpes simplex virus, HPV-Human papilloma virus, HIV-Human immunodeficiency virus.
*(Figures are rounded)

RTIs and Contraception:

Intrauterine device (IUD) has been implicated in the development of PID, with the risk being maximum in the immediate post insertion period (first 30 days). The estimated R.R. of PID developing in an IUD wearer is 2-4 times that of a nonwearer utilizing no contraceptive method and may be as high as 7-9 fold greater in nulliparous women. However this risk is lower in married women with a stable sexual relationship.

Several studies (Germain 1992, Gerbase, 1998) have shown a decrease in risk of PID in users of hormonal contraceptives including injectable and implants. Progestogen-induced increase in density of cervical mucus and decrease in volume as well as duration of menstrual blood flow prevents ascent of organisms from the lower genital tract.

Barrier methods of contraception also display a protective effect (R.R. = 0.6) against development of PID when compared to no contraceptive use. They also have a role in preventation of HIV infection & AIDS as in protection against viral STDs with their sequelae of carcinoma cervix.

Diagnosis of RTIs:

RTIs have been categorized by international and national agencies like CDC, WHO & NACO in various syndromes that facilitate its diagnosis and management. These include genital ulcer syndrome, urethral discharge syndrome, vaginal and cervical discharge syndrome, inguinal swelling syndrome, and lower abdominal pain.

At the primary health care level, the health personnel can be trained to recognize the quality of discharge, measurement of pH and clinical identification of other signs of these infections. Light microscopic examination of wet vaginal smear would diagnose vaginitis caused by Candidiasis, Trichomoniasis and Bacterial vaginosis. This can easily be done at the secondary level of health care. Stained smears (Gram smear, Giemsa smear) help diagnose Gonorrhoea, Chancaroid, Donovanosis and Mycoplasma infections. Papanicolaou (Pap) smears in addition may indicate an underlying infection like Trichomoniasis, Chlamydia, HSV and HPV. Serological tests for diagnosis of Syphilis and HIV are also now freely available at secondary health care level. In tertiary institutes the use of more advanced diagnostic techniques would help specific diagnosis of infections like Syphilis, HSV, HPV, Chlamydia, HIV (Dyck, 1999). HPV typing and its oncogene detection (E6, E7) may help in identifying patients at high risk for cervical cancer.

Pelvic inflammatory disease and its diagnosis

Pelvic inflammatory disease is defined as infections of the upper genital tract, caused by spread of

microorganisms from the vagina or cervix to the endometrium, fallopian tubes and/or continuous structures. In developing countries, exact quantification is difficult but a prevalence of around 25% in patients with gynaecological disorders has been reported (Bang, 1989). Diagnosis of acute PID is clinical. Minimum criteria for diagnosis of PID are lower abdominal pain, adnexal tenderness, and cervical motion tenderness. Additional criteria that support the diagnosis of PID includes fever (temperature > 101°F), abnormal cervical or vaginal discharge, leucocytosis, elevated ESR, elevated C-reactive protein (Centre for Disease Control and Prevention, 1998).

Management of RTIs and Prevention of its Complications

Early diagnosis and prompt treatment with modern antibiotics and antiviral drugs restricts the spread of lower genital tract infections and their sequelae. Simultaneously steps should be taken to trace and treat the sexual partner so as to prevent reinfections. Reproductive Health Care programs should encourage male participation. AIDS epidemic has brought to light the health consequences of male participation. AIDS epidemic has brought to light the health consequences of male risky sexual behavior. Strategy to reach out to men have to be pursued at the community level. A WHO study group on management of patients with STDs has recommended that prior to treatment these aspects of STDs should be discussed with the patient. However, some of these involve delicate marital, familial and community issues and are difficult to address in the Indian context. Care should be taken whilst counselling not to disrupt marital harmony. In institution-based services however, these issues can be handled professionally in collaboration with social scientists. A greater awareness and some informal training to medical professionals in handling these issues can go a long way.

Drug Treatments for RTIs

In India, facilities for diagnosis may not be adequate at the primary health care level; hence a syndromic approach to management can be used. Treatment of RTIs by syndromic approach:

Genital ulcer syndrome-treat for chancroid and syphilis, treatment for donovanosis is added in places with high prevalence of this disease (e.g. South India).

Urethral discharge syndrome- treat for gonorrhoeal and chlamydial infections and for trichomoniasis in case of treatment failure.

Vaginal and cervical discharge syndrome- treat for gonorrhoeal, chlamydial, trichomonial infections and for bacterial vaginosis, unless discharge appears like thrush, in which case only treatment for candida albicans is given.

Lower pelvic pain-treat for gonorrhoea, chlamydia, Anaerobic bacteria, T. vaginalis and bacterial vaginosis. Inguinal bubo- treat for chancroid and lymphogranuloma venereum.

Single Dose Preparations / Short Regimens

Many single dose preparations or short regimens and combination therapy are now being marketed in order to simplify treatment and improve compliance. They are useful in uncomplicated cases, early cases and those with a good tolerance for drugs. The success rate is usually slightly lower than the full-fledged treatment course of 1 to 3 weeks. These should be avoided in pregnant women (unless noncompliance is suspected) or in PID cases. In PID longer duration of treatment and more intensive treatment is required as outlined later.

The Centre for Disease Control's (CDC latest treatment recommendations are as follows (vide infra) (CDC, 1998).

1) Gonorrhoea:-

Cefixime 400 mg single oral dose or Ceftriaxone 125 mg single IM dose or Ciprofloxacin 500 mg single dose or Ofloxacin 400 mg single oral dose.
Patients infected with N. gonorrhoea are often co-infected with Chlamydia trachomatis, hence should be routinely also treated with Azithromycin 1 gm single dose or Doxycycline 100 mg twice daily orally for 7 days.
In pregnancy, patients should be treated with Cephalosporins and if patients are intolerant then Spectinomycin 2 gm IM single dose can be given.

2) Chlamydia :-

The recommended regimens are:
Azithromycin 1 gm single oral dose or Doxycycline 100 mg twice daily orally for 7 days or Erythromycin stearate 500 mg four times daily orally for 7 days.
Alternative regimes include Ofloxacin 300 mg twice daily

orally for 7 days. In pregnancy, Erythromycin stearate 500 mg four times daily for 7 days is recommended.

3) Syphilis :-

In early syphilis Benzathine penicillin G 2.4 mIU single IM dose is the recommended treatment. Alternative options for treatment include Doxycycline recommended 100 mg twice daily for 2 wks. or Tetracycline 500 mg four times daily for two wks. In syphilis of more than one-year duration the penicillin has to be given weekly for 3 doses. In pregnant women with syphilis the same doses of penicillin are suggested. If the woman has penicillin allergy, desensitization and then treatment with penicillin is preferred over other regimes. Ampicillin 500mg with probenecid 500mg two times a day for 2-3 weeks can also be considered.

4) Granuloma inguinale: -

The recommended regimes are Trimethoprim 80 mg / sulpamethoxazole 400 mg 2 tablets twice daily for 3 weeks or Doxycycline 100 mg twice daily for 14 days. Alternative regimes include Ciprofloxacin 750 mg twice daily orally for 3 weeks or Erythromycin 500 mg four times / day for 3 weeks.
In pregnancy, Erythromycin 500 mg four times daily for 3 wks and in addition an aminoglycoside like Gentamycin 1 gm / kg I.V. every 8 hours should be strongly considered.

5) Lymphogranuloma venereum:-

Doxycycline 100 mg twice daily or Erythromycin 500 mg four times daily for 3 weeks is suggested. In pregnancy Doxycycline is contraindicated.

6) Chancroid:-

Azithromycin 1 gm single oral dose or Ceftriaxone 250 mg single IM dose or Ciprofloxacin 500 mg twice-daily dose for 3 days or Erythromycin 500 mg four times daily for 7 days can be given.

7) Genital herpes:

Acyclovir in doses of 400 mg thrice a day or 200 mg five times a day for 7 to 10 days or until clinical resolution is recommended for initial episodes. For severe disease 5-10 mg / kg of body weight IV every 8 hour for 5-7 days or till clinical resolution should be given.

For recurrent episodes 200 mg five times a day or 400 mg thrice daily or 800 mg twice daily of Acyclovir or Famciclovir in dose of 125 mg twice daily orally or Valacyclovir 500 mg twice daily orally for 5 days should be given.

Acyclovir is not recommended in pregnancy but an ongoing register has not shown any birth defects in babies born to mothers treated for life threatening herpes with the drug.

8) Bacterial vaginosis:

Recommended regimens include Metronidazole or Tinidazole 500 mg twice daily orally or Clindamycin cream 2% 5gm intravaginally at bedtime or Metronidazole gel 0.75% 5gm intravaginally twice daily for 7 days. Alternatively Metronidazole can be given in a 2gm single oral dose or Clindamycin can be given orally 300 mg twice daily for 7 days. Both drugs are safe for use in pregnancy in the 2nd and 3rd trimester.

9) Trichomoniasis:

Metronidazole 2 gm single oral dose is recommended in non-pregnant adult and pregnant patients. Alternatively Metronidazole or Tinidazole 500mg twice daily for 7 days can also be prescribed.

10) Candidiasis:

Intravaginal agents like Butoconazole 2% cream (5gm) for 3 days or Clotrimazole 1% cream (5gm) for 7-14 days or Clotrimazole 100 mg vaginal tablet for 7 days, 200mg 2 tablets for 3 days or 500mg tablet single application or Miconazole 2% cream (5gm) are the first choice drugs in adults and the only ones recommended in pregnancy. Alternative treatment options include Mycostatin vaginal pessaries or cream or Fluconazole 150mg single oral dose. Itraconazole 200 mg daily x 3 days can be used in resistant cases.

Treatment for PID:

PID treatment regimens must provide empiric broad-spectrum coverage of likely pathogens and treatment must start on clinical suspicion without waiting for bacteriologic confirmation of diagnosis so as to limit the sequalae of PID.

Whether oral outpatient therapy is sufficient or hospitalization and parenteral therapy is required

depends on the following criteria.

Criteria for hospitalization:

a. When surgical emergencies such as appendicitis cannot be excluded.
b) Patient has a pelvic abscess
c) Patient is acutely ill presenting with nausea/vomiting or high fever
d. Patient does not respond clinically to oral antimicrobial therapy or is unable to tolerate oral regimen.
e. The patient is pregnant.

Out patient treatment for PID:

Regimen A: Ofloxacin 400mg twice daily plus Metronidazole Tinidazole 500mg twice daily for 14 days.
Regimen B: Ceftriaxone 250 mg IM single dose or Cefoxitin 2 gm IM single dose plus Doxycycline 100 mg twice daily for 14 days. (Other parenteral Cephalosporins e.g. Cefotaxime or Ceftizoxime can also be used).

Parenteral Treatment:

There are no efficacy data comparing parenteral with oral regimes and most trials have used parenteral treatment for at least 48 hours after the patient has demonstrated substantial clinical improvement (CDC, 1998). The parenteral regimes include:

Regimen A: Cefotetan 2 gm IV every 12 hrs. or
Cefoxitin 2 gm IV every 6 hrs plus
Doxycycline 100 mg IV or orally every 12 hrs.

Oral therapy with Doxycycline 100 mg twice daily can be started 24 hrs after the patient shows signs of clinical improvement and should be continued for 14 days.

Regimen B: Clindamycin 900 mg IV every 8 hrs plus Gentamycin 2mg/kg IV or IM followed by 1.5 mg/kg 8 hourly

After the patient improves clinically, oral treatment with Clindamycin 450mg four times daily plus Doxycycline 100mg twice daily should be given to complete a total of 14 days therapy. When tubo ovarian mass (TO mass) is present regimen B is preferred but if regimen A is followed, Clindamycin (450 mg four times daily) or Metronidazole (400 mg three times daily) should be added to Doxycycline. Surgical intervention is required for a TO mass only if patient fails to respond to medical treatment or in cases of ruptured TO abscess. It may be necessary to treat severe or chronic PID for a total duration of 3 weeks.

Newer Developments in Diagnosis and Management

Diagnosis:

Recent studies have revealed the importance of microbiological culture studies (6 species of Candida, H_2O_2 producing lactobacilli) newer diagnostic techniques like Polymerase chain reaction (PCR), Ligase chain reaction (LCR), Direct fluorescent antigen antibody test (DFA), and newer ELISAs.

Immunomodulation:

Herpes simplex vaccines subunit glycoprotein vaccines are under phase III clinical trial.

Human Papilloma virus vaccines trials are currently underway.

Barrier methods of RTIs prevention:

Newer local microbicides which may be spermicidal/non-spermicidal (antibiotics, antiseptic, herbal derivatives and other bio-acceptable materials are being explored eg. Vaginal Microbicidal Formulation Workshop proceedings, 1997. Newer designs and materials for male, female condoms are being developed and may significantly reduce the risk of RTI transmission and spread.

Newer Drugs:

Attempts are being made to understand the metabolism, enzyme systems and molecular biology of various organisms so that specific and more potent drugs can be developed (Petrin, 1998).

Role of Alternative Medicine:

In ancient Ayurvedic literature there is a mention of use of medicinal plants for the treatment of RTIs. Recently, modern ayurvedic physicians and other scientists have shown the benefits of ayurvedic formulations with several delivery systems in control of vaginal infections. Such delivery systems include oral tablets and liquids, local preparations like douch with decoction, medicated tampons, pessaries,

suppositories. Different parts of medicinal plants (roots, leaves, flower or bark) like Vada (Ficus bengalensis), Peepal (Ficus racemosa), Lodhra (Symplocos racemosa), Shatavari (Asparagus racemosus) have been recommended for use in treatment of leucorrhoea (Khan and Javed, 1998). Some of these are currently under investigation using modern methodologies.

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