Clinical Review

Clinical Review identifies issues in the medical literature of interest to clinicians in Africa. Essential references are given at the end of each section

STI Review

Sexually transmitted infections and infertility

Worldwide, an estimated 50–70 million couples suffer from infertility.[1,2] Most of these couples live in developing countries. Childlessness can be devastating, and has many repercussions, especially in developing countries. Infertility is associated with marital instability, loss of social status, social isolation, economic insecurity, guilt, depression, suicide, and violence. Indeed, for many couples, being childless is devastating.

Accurately estimating the prevalence of infertility is difficult, in part due to varying definitions.[3] The usual clinical definition identifies primary infertility as no conception after 12 months of regular, unprotected sex. Epidemiological studies extend this period to 24 months. Instead of conception, demographers focus on live births, and often define infertility as no live birth for a woman in a steady relationship, desiring a child, not using contraception, over a 5- or 7-year period. Secondary infertility refers to the inability to conceive after a previous live birth. These definitions are also problematic because they focus on women, and an outcome of conception or live birth, and do not include analysis of both female and male factors in infertility. Given the devastating effects of infertility on couples' lives, it has been suggested that it would be more appropriate to let women self-define infertility, as the best measure linking infertility to social outcomes.[4]

A demographic analysis of the trends in infertility worldwide found levels essentially unchanged between 1990 and 2010.[3] In 2010, 1.9% of child-seeking women aged 20–44 years of age were unable to have a first live birth after 5 years, and 10.5% of child-seeking women with a prior live birth were unable to have an additional birth – a total of almost 50 million women. In sub-Saharan Africa, the study found 2.8% of women were infertile in 1990 and this declined to 2.0% in 2010. However, the total number of infertile women in the region increased due to population growth. The few studies on the 12-month prevalence of infertility in sub-Saharan Africa indicate levels ranging from 9% in the Gambia to 30% in Nigeria.[1] These 12-month prevalence levels are naturally higher, given the shorter time period.

It is estimated that about one-third of infertility in couples is due to male factors, one-third due to female factors, and one-third relates to a combination of male and female factors.[5] The most significant cause of female infertility in sub-Saharan Africa is bilateral tubal occlusion due to sexually transmitted and pregnancy-related infections.[1] One study found over 85% of women in Africa had a diagnosis of infertility attributable to infection compared with 33% of women worldwide.[1] Post-partum and post-abortion infections are associated with female infertility.

Chlamydia trachomatis and Neisseria gonorrhoeae are the organisms most commonly associated with fertility problems. These bacteria affect the male genitourinary tract and the female reproductive system. *C trachomatis* infection is often asymptomatic in both men (50% of cases) and women (70–80% of cases), but has a much greater effect on women. Chlamydial infection can cause tubal lacerations and obstruction, ectopic pregnancy, and can result in pelvic inflammatory disease (PID), peritonitis, and adhesions.[6] In men, *C trachomatis* is the most common cause of non-gonococcal urethritis, and can cause epididymitis-orchitis, prostatitis and sperm tract obstruction. Chlamydia is also associated with a three- to four-fold increased risk for transmission of HIV, and increased risk of cervical carcinoma.[7] *N gonorrhoeae* causes urethritis in men and urethral and endocervical infection in women. Ascending infection occurs in 10–20% of women and can result in PID and infertility. *N gonorrhoeae* infection is asymptomatic in 30–80% of women and 5% of men.[8] Both *N gonorrhoeae* and *C trachomatis* infections are associated with premature rupture of membranes in pregnancy. Bacterial vaginosis, which is an alteration of the normal vaginal flora, is also associated with cervicitis, endometritis, salpingitis, and PID. An estimated one in four women with PID will develop infertility.[8]

Studies show that viral infections can impair sperm, causing infertility. It is known that HIV, hepatitis B, and hepatitis C affect sperm and reduce their forward motility. Less is known about the effects of semen infection with human papillomavirus (HPV), herpes viruses (HSV), cytomegalovirus (HCMV), and adeno viruses (AAV), but these viruses are thought to play a major role in male infertility.[9]

Many other pathogens that cause sexually transmitted infections likely have a role in infertility, but their specific contribution requires more research. For example, *Mycoplasma genitalium, Mycoplasma hominis, Ureaplasma urealyticum, Escherichia coli, Trichomonas vaginalis, Candida,* HPV, and HSV are all associated with infertility.[6]

Diagnosis and treatment

Fortunately, *C trachomatis, N gonorrhoae, Mycoplasma, T vaginalis,* and *candida* all respond to treatment.[8] However, the accurate diagnosis of these infections in low-resource settings still relies on syndromic management protocols and laboratory testing. Syndromic management is notoriously inaccurate for vaginal discharge, especially in adolescents. Regular screening of patients has not been feasible in most settings, but newer rapid diagnostic tests are being developed.

C trachomatis can be treated with azithromycin 1 g, single dose orally, or doxycycline 100 mg, orally, twice daily for 7 days. *N gonorrhoae* is becoming more difficult to treat, but ceftriaxone 125 mg IM, single dose

or, where quinolone antibiotic resistance is not present, fluoroquinolone single dose. Because antibiotic resistance varies with location and over time, it is important to check with the latest local treatment protocols.

Prevention

Prevention of STIs and pregnancy-related sepsis are key to decreasing infertility. Prevention strategies need to be appropriate to the target group, and help them overcome the risks they face. One study of women with tubal infertility showed that when compared with fertile controls, the infertile women were younger at first intercourse, were more likely to have had first intercourse pre-menarche, had more sexual partners, more abortions before marriage, more induced abortions, were more likely to have been diagnosed with STIs, and had fewer years of schooling.[1] The sexual and reproductive events of the teenage years often determine future fertility. A study of women's understanding of reproductive tract infections (RTIs) among reproductive age women in Lagos, Nigeria found that most women had heard of RTIs, and about one-third had experienced symptoms, mostly vaginal discharge, in the prior month.[10] The women had poor knowledge of the risks of acquiring an RTI, with more women choosing toilet (45%) than sexual intercourse (44%) as the mode of transmission. Few women associated unsafe abortion (20%), unsafe delivery (17%), and genital tract procedures (14%) as modes of acquiring RTIs.

There are currently vaccines available to protect against hepatitis B and HPV. The hepatitis B vaccine has been successfully integrated into infant immunization programmes in more than 90% of countries worldwide, largely to prevent deaths from chronic liver disease and cancer.[11] HPV immunisation is established in about 45 countries, mostly middle- and high-income. Increasing the availability and routine vaccination of women and men against HPV could save millions of lives in low-income countries. Research into vaccines against herpes and HIV is advanced, although no effective vaccines are yet available. Research into vaccines against chlamydia, gonorrhoea, syphilis, and trichomoniasis is in earlier stages of development. Male circumcision has been shown to reduce men's risk of acquiring HIV and may offer some protection against herpes and HPV. Research into tenofovir, a microbicide gel, shows promise for averting HIV infection in women.

Treating infertility

Treating infertility often relies on assisted reproductive technologies, including *in-vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI). Neither of these treatments is widely available in sub-Saharan Africa. Infertility treatment has been neglected, with a focus instead on the perceived more acute needs for contraception, and prevention of HIV/AIDS and maternal mortality. However, in the last two decades, infertility and the idea that reproductive rights must include the right to control fertility as well as the right to assist fertility has gained global acceptance and support.[12] Nonetheless, diagnosis and treatment care for infertility in sub-Saharan Africa is often incomplete, rudimentary and offered in unsystematic and irregular ways. More effective care is often limited to the private sector in capital cities.[12] In the public sector, the outdated and dangerous use of dilation and curettage (D&C) to treat infertility continues, in part because healthcare providers have not received any updated training in infertility treatment.

Just as there has been some progress in developing STI testing and treatment more appropriate to low-resource settings, simplified diagnostic and treatment options for infertility are increasing. While explanation of the options being developed is beyond the scope of this review, a good summary is available by Ombelet, co-coordinator of the European Society of Human Reproduction and Embryology.[13,14] There are many issues that surround infertility treatment in developing countries, including whether they can be cost-effective, who should be offered services (HIV-positive women? Should cryopreservation of embryos be offered? etc.), and how can quality care be introduced.

Prevention and education remain the most important steps in addressing infertility, and women and men need to be educated about risks and preserving fertility.

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Ophthalmology Review

Corneal disease

Corneal disease remains a major cause of blindness in Africa. Historically the majority of corneal scars have been caused by trachoma, onchocerciasis, and vitamin A deficiency. Happily these conditions are becoming less common thanks to public health interventions such as vitamin A and ivermectin distribution, measles immunisation, and improved sanitation and water supplies. The World Health Organization estimates that about 5% of global blindness is due to corneal opacity not caused by the above three conditions, however in East and Central Africa, this rises to 12%. Millions more are blind in one eye. Much of this corneal scarring is caused by microbial keratitis.

Microbial keratitis appears to be more common in the tropics than in temperate climates. Two studies from south Asia estimated the incidence at between 100 and 800 per 100 000 population per year. These estimates are at least ten times higher than the incidence in the EU or North America. Microbial keratitis is disproportionately more common in poor and rural communities, as it is frequently associated with minor eye injuries sustained during agricultural activities. The prognosis for microbial keratitis appears to be worse in Africa than in developed countries. A team from Kilimanjaro Christian Medical Centre (KCMC), in north Tanzania, investigated why this might be the case[1].

They looked at all cases of microbial keratitis admitted to the eye ward over a 27-month period. 170 cases were identified. The median interval between onset of symptoms and presentation to KCMC was 14 days. However many patients had visited another health facility prior to attending KCMC. For these patients, the median duration of symptoms was 21 days, compared with 8 days in those who presented directly to KCMC.

Some 92 people had received treatment before coming to KCMC. Of these, 59 had received probably ineffective treatment, such as topical chloramphenicol or tetracycline eye ointment.

The spectrum of disease was far more severe than is encountered in rich countries. The average ulcer diameter was 5.3 mm – roughly half the diameter of the cornea; 37% had a hypopyon, and 19% of the corneal ulcers were perforated at presentation, and another 11% perforated following admission.

Only 63 eyes had microbiological investigation, which yielded positive results in about 50% of cases. Half of these showed fungi. Because of the high prevalence of fungal keratitis, all eyes were treated with hourly topical ciprofloxacin and natamycin. About 80% of ulcers eventually healed, but only 33% of the eyes had a vision of 6/60 or better at discharge, compared with 19% at admission. Worse outcomes were associated with large (>5 mm diameter) ulcers, and delayed presentation to KCMC.

Although this case series comes form a tertiary unit, and is undoubtedly biased towards more severe presentations, it is very similar to my own experience in Kenya and Tanzania, and confirms that microbial keratitis in Africa tends to be severe, and frequently leads to loss of sight in the affected eye.

Attendance at another health facility prior to admission to KCMC was associated with worse outcomes. In most cases patients had been treated with inadequate antibiotic regimens such as chloramphenicol eye drops or tetracycline eye ointment. These are sufficient for treating conjunctivitis, but will not be effective in established microbial keratitis. Inadequate antibiotic therapy merely delays effective treatment and allows the infection to become established in the deep stroma.

A further weakness of treatment in other health facilities was that very few of them had access to topical anti-fungals, and half of the cases with positive microbiology were due to fungi.

What is the best treatment for fungal keratitis?
A recently published clinical trial from south India concluded that natamycin appears to be better than voriconazole.[2] The authors recruited 323 patients with fungal keratitis, proven by observation of fungal hyphae on microscopy of a corneal scraping.

Patients and observers were masked to treatment allocation. This can be difficult to achieve, as natamycin is a suspension but voriconazole is a clear solution. In this trial both drugs were packaged in identical opaque bottles, and, following treatment, the eye was irrigated with normal saline prior to examination by the trial ophthalmologists. All patients were treated with hourly eye drops (during waking hours) for 1 week, and then 2-hourly drops for a minimum of 3 weeks after enrollment

Unlike many trials of treatment for corneal ulcers, the primary outcome was not time to healing, but visual acuity at 3 months – a much more important endpoint for the patient. Secondary outcomes included perforation/therapeutic penetrating keratoplasty, time to healing, and microbiological cure at 6 days.

Culture showed that 40% of the ulcers were due to *Fusarium* species. *Aspergillus spp* caused another 17% of infections, and in 20%, the fungus could not be cultured.

At 3 months after enrolment, patients treated with natamycin had 1.8 lines better vision than those treated with voriconazole. The mean visual acuities were approximately 6/15 in the natamycin-treated eyes compared with about 6/24 in the voriconazole group. The data and safety monitoring committee stopped the trial after 323 patients had been recruited when they found that 34 perforations had occurred in eyes treated with voriconazole and 18 in eyes randomised to natamycin (p=0.02)

The time to healing was fairly similar in both groups, although the duration of treatment was shorter (31 days) in the natamycin group compared with the voriconazole arm (39 days). Ulcers were slightly more likely to heal with natamycin than voriconazole and corneal scars were slightly smaller in natamycin-treated eyes.

Almost all of the benefits of natamycin treatment were due to its significantly greater effect in *Fusarium* ulcers, where it performed much better than voriconazole. For example, in Fusarium infections, the 3-month visual acuity was four lines better for the natamycin

group than the voriconazole arm. In non-*Fusarium* ulcers, there was little difference between the two agents.

Although this is a very well-designed clinical trial, with no obvious sources of bias, there are some limitations. All the patients were recruited in south India. Patients in Africa may respond differently, and the proportion of ulcers caused by *Fusarium* may be different in different geographical regions. Comparing the characteristics of the ulcers recruited to this trial, with those from the study in Tanzania, the ulcers in this trial appear to be less severe. However, it is hard to disagree with the authors' conclusion that natamycin is the treatment of choice for filamentary fungal keratitis. It is also likely to be considerably less expensive than voriconazole.

Natamycin eye drops can be obtained from India, and are included in the IAPB Standard List of eye equipment. They cost around US$5–10 per bottle. Given that treatment must be continued for 30 days, this is not cheap. However, as the alternative is almost certainly loss of vision in the affected eye, this represents a very cost-effective intervention.

The corneal scarring following infectious keratitis is partly the result of damage by the infecting microorganism and partly due to the host's inflammatory and immune reaction against the infective agent. It has been suggested that topical steroids to suppress the inflammation may be beneficial in bacterial keratitis. This was tested in a randomised clinical trial[3].

The study recruited 500 patients with culture-proven bacterial keratitis. They were all treated with 48 hours of hourly moxifloxacin, followed by either topical prednisolone or placebo, four times per day for 1 week, then twice a day for 1 week. The moxifloxacin was continued every 2 hours until the ulcer healed.

The main outcome measure was the visual acuity at 3 months after recruitment. The median visual acuity at baseline was approximately 6/36 in both groups and at 3 months, it was about 6/15 in both groups. Time to healing was about 7 days in both groups. The number of ulcers perforating or requiring therapeutic keratoplasty was also similar in both groups.

However, the study pre-specified sub-groups, by visual acuity at presentation, and by ulcer location, size, and depth. In eyes with a baseline vision of CF or worse, and in eyes in which the ulcer affected the entire central 4 mm of the cornea the visual acuity in the steroid arm was 1.7 and 2.0 lines better respectively.

This study suggests that a modest dose of topical steroid may be valuable in patients with the most severe bacterial corneal ulcers.

There are some important caveats to this study. Firstly, all the ulcers were given 48 hours of intensive broad-spectrum antibiotic treatment. Moxifloxacin is a relatively costly eye drop, and is unlikely to be widely available in Africa. It is not clear that similar results would be obtained if the ulcer was treated with other topical antibiotics. Secondly, the ulcers included in the study appear to be less severe than those encountered in the series from Tanzania. A relatively modest does of topical steroid was used in order to reduce the risk of adverse effects. It is possible that more intensive treatment might be more effective, but this would also carry a greater risk of side-effects. Finally, none of the ulcers had any fungal infection.

If you have the facility to examine corneal scrapings for fungi, and can be confident that you are dealing with a purely bacterial infection, there is a case for adding steroid to the treatment of the most severe ulcers, which either involve the central visual axis, or have caused loss of vision to counting fingers or less. However, this should only be done after the ulcer has been intensively treated with topical broad spectrum antibiotics for at least 48 hours.

If you cannot exclude fungal corneal ulcers, it may be sensible to treat all microbial keratitis with both an anti-fungal – preferably natamycin – and a broad spectrum antibiotic such as a fluoroquinolone. In these circumstances I would avoid using topical steroids.

Perhaps most important of all is to ensure that you can recognise microbial keratitis, and differentiate it from other more common, but less dangerous, causes of acute red eye.

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Africa HEALTH CPD Challenge
See page 53 for questions about this article