Review IVF: how can we reduce the risks of infection?

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During *in vitro* fertilisation the female partner undergoes procedures that carry a risk of pelvic infection, such as oocyte recovery and embryo transfer. When sperm is present in the ejaculate, the male partner avoids the risk of iatrogenic infection. If sperm is retrieved directly from the epididymis or testis, the male partner's recovery may also be complicated by infection. Although rare, infections resulting from *in vitro* fertilisation can be devastating to those affected. This article looks at ways in which the risk of infection can be reduced, both by good clinical technique and by using antibiotic prophylaxis.

Keywords antibiotics / assisted conception / infection / *in vitro* fertilisation / pelvic inflammatory disease

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Introduction

Many couples will undergo a battery of fertility investigations before their referral for *in vitro* fertilisation (IVF). Some investigations, including hysteroscopy and diagnostic laparoscopy, involve instrumentation of the uterus. This carries a risk of ascending pelvic infection, particularly in women where the cervical canal is infected with *Chlamydia trachomatis*. The National Institute for Health and Clinical Excellence (NICE) guidelines on fertility[1] recommend that women should be offered screening for *C. trachomatis* using an appropriately sensitive technique before uterine instrumentation is performed. Where screening has not been performed, prophylactic antibiotics should be offered.

This article focuses on the prevention of infection from procedures performed as part of IVF treatment, concentrating on the clinical, rather than the laboratory, aspects of IVF.

Transvaginal ultrasound scanning

During IVF, gonadotrophins are administered to stimulate the ovaries. The multiple follicles that develop are counted and measured by transvaginal ultrasound scans. The vaginal probe is covered with a disposable cover or condom, which is changed after each examination. Studies[2,3] have shown that 0.9–2% of condoms have perforations when inspected after use. Thus, there is the potential for sexually transmitted infections to be passed from one woman to another. Regular disinfection of the probe using isopropyl alcohol wipes has been shown to reduce the risk of contamination,[3] although the wipes may not be suitable for all machines. Operators should consult individual hygiene instructions to ensure that damage to the transducer membrane does not occur.

Oocyte collection

Oocyte collection is usually performed transvaginally using ultrasound guidance. When the ovaries are inaccessible by this means, eggs may be collected directly through the abdominal wall, through the urinary bladder or laparoscopically.

For most women, transvaginal egg collection (TVEC) is a simple process which is usually performed under conscious sedation. Opinion is divided about whether the vagina should be prepared with a topical antibacterial agent before commencing egg collection. While povidone-iodine and chlorhexidine solutions have been used with success, many operators have found such precautions unnecessary. In addition, some authors have suggested that pregnancy rates are lower when iodine-containing solutions are employed.[4] While most operators using topical antibacterials describe flushing the vagina with water or saline after use, it is difficult to imagine that all of the solution is removed. It is also hard to believe that any topical solution will remove all micro-organisms from the vaginal fornices of a conscious woman.

A sterile, hollow needle guide is attached to the vaginal ultrasound probe, over the top of a sterile condom. An aspiration needle is passed down the lumen of the needle guide and the ovarian follicles are drained under ultrasound guidance. It is important to keep the aspiration needle sterile by using a no-touch technique. It is also wise to avoid multiple vaginal punctures, especially when endometriomas are present. Endometriomas should not be punctured as their contents would be expected to encourage the multiplication of pathogens.

When the aspiration needle penetrates the vaginal wall, vaginal microbes may be transferred into the peritoneal cavity and adnexae. Such microbes may be dealt with by the natural defence mechanisms, they may be eradicated by prophylactic antibiotics, or they may colonise and cause infection. Pelvic infection following TVEC is rare, whether antibiotics are used or not. In a series of 2670 procedures published by Bennett *et al.*[5] in 1993, the incidence of pelvic infection was 0.6% without antibiotic prophylaxis. Half of these infections were classified as severe, with pelvic abscess formation. In the same year, Tureck *et al.*[6] found the post-TVEC infection rate in 674 women to be 1.3%. In their study, women were given intravenous cephalosporins or oral doxycycline. The use of antibiotic prophylaxis for TVEC remains controversial, with wide variations in clinical practice. In our own survey of UK IVF clinics,[7] we found that 57% gave the female partner some antibiotic prophylaxis during treatment. Common choices were rectal metronidazole, intravenous co-amoxiclav and oral doxycycline. Some clinics gave the antibiotics prior to the TVEC, some at the procedure and some afterwards.

Women with a history of previous pelvic inflammatory disease (PID) and/or adnexal adhesions are at greater risk of complications from TVEC. There is widespread supposition that this is due to the reactivation of chronically infected adnexae. There are many reports of abscesses caused by TVEC. These may be ovarian (originating in and affecting only the ovary), tubo-ovarian, or widespread within the peritoneal cavity. Extensive sepsis can be life threatening. If conception occurs when infection and pyrexia are present the pregnancy may be jeopardised. There are, however, reports of ongoing pregnancies and live births following treatment cycles complicated by infection, even when surgical drainage has been required for resolution.[5,8] Drainage can be

performed by laparoscopy, laparotomy or colpotomy.

Occasionally during TVEC the needle tip overshoots into the surrounding structures, including the bowel. Fortunately, resulting infections are thought to be rare. In 1992, Van Hoorde *et al.*[9] reported a case of appendicitis following TVEC. Puncture holes were found in the appendix, leading the authors to conclude a causal relationship between the two events.

When there is concern about introduction of infection into the pelvis during TVEC, particularly when there is a previous history of pelvic infection/abscess following a TVEC, transabdominal egg collection may be preferable. The reported complication rate following transabdominal egg collection is low.

Sperm collection

Most men are able to provide a semen sample by ejaculation. They should be instructed to wash their hands and genitals with soap and water, and then dry them before masturbating into a sterile container.[10] Even when good hygiene is adopted it is not uncommon for micro-organisms to be present in semen and this does not always indicate infection. Bacteriospermia can be attributed to pathogens but also to contamination or commensals. Cottell *et al.*[11] found that fertilisation, cleavage and pregnancy rates were independent of microbial presence. Liversedge *et al.*[12] concluded that treatment of asymptomatic men with positive semen cultures was unnecessary. The same authors also highlighted the potential detrimental effect of such treatment. They postulated that antibiotics administered to the male partner might be excreted in semen, ejaculated during intercourse and might alter vaginal flora. This could result in a relative overgrowth of potentially pathogenic organisms.

Men who are unable to ejaculate or who are azoospermic may undergo a procedure to retrieve sperm surgically and the sperm collected can be used for intracytoplasmic sperm injection. For men with obstructive azoospermia, percutaneous epididymal sperm aspiration (PESA) or microsurgical epididymal sperm aspiration (MESA) may be attempted. For non-obstructive azoospermia, testicular sperm aspiration (TESA) or testicular sperm extraction (TESE) are required. All procedures can be performed under local or general anaesthesia. For PESA or TESA, only fine needle punctures of the tissues are performed, so little is left in the way of a resulting wound. Small testicular biopsies can be taken using a large-core (e.g. 14 gauge) biopsy gun and sutures are not needed. MESA and large TESE procedures require an incision to be made in the scrotum, which must be closed at the end of the procedure.

Although there have been several studies comparing different methods of surgical sperm retrieval, little has been published about antibiotic prophylaxis or postoperative wound infection rates. Wood *et al.*[13] looked at postoperative pain, complications and satisfaction rates in men who underwent surgical sperm retrieval. They gave men undergoing either PESA or TESE a five-day course of prophylactic flucloxacillin or erythromycin. They found that bleeding and bruising were more common in men with larger testes and suggested that this may reflect the increased vasculature and blood flow in these men. The investigators did not ask specifically about postoperative wound infection. Schlegel *et al.*[14] evaluated 64 men undergoing TESE and followed them up at one, three and six months. To our knowledge, antibiotics were not given. None of the men reported a wound infection.

Embryo transfer

In a fresh IVF treatment cycle embryos are usually replaced two, three or five days following TVEC. A bivalve speculum is inserted into the vagina and the cervix cleansed. The embryos are loaded into a fine plastic catheter, which is passed through the cervical canal into the endometrial cavity. A plunger is depressed to expel the embryos. Embryo replacement involves breaching the cervical mucus barrier and can, therefore, transfer microbes from the lower genital tract into the uterine cavity. Uterine instrumentation may provoke ascending *C. trachomatis* infection in women who carry the organism in their cervix. The question of whether to screen women before they embark on treatment, or whether to offer antibiotic prophylaxis to all, has been hotly debated by fertility specialists. This division of opinion appears to be reflected in clinical practice.

In our survey in 2002,[7] we found that 33% of IVF clinics opted to screen for *C. trachomatis*, while 14% gave treatment to all. More than half of the clinics that responded were neither screening nor routinely covering women for this infection. We would expect to find that practice has changed since the publication of the NICE guidelines in 2004.[1] We believe that clinicians may feel confused about which is the best test for them to use for *C. trachomatis* screening. Factors such as cost, sensitivity and ease of performing the test must all be considered.

Local practice is likely to be dictated ultimately by microbiologists, rather than IVF clinicians. Nucleic acid amplification tests such as polymerase chain reaction (PCR) and ligase chain reaction (LCR) can be used on endocervical swabs or urine samples. Sensitivities exceed 85%. Cell culture and enzyme immunoassay, which can also be performed on endocervical swabs, are significantly less sensitive. A

small proportion of women will carry *C. trachomatis* only in the urethra and these cases will be missed by endocervical sampling alone. To complicate matters further, women can screen negative for cervical colonisation, yet have viable chlamydial infection further up the genital tract (for example, in the fallopian tube). This may persist for some years after the initial infection and may be reactivated by uterine instrumentation. This phenomenon has led some authors to recommend screening for old chlamydial infection by testing for serum IgG antibodies to *C. trachomatis*, as well as looking for active disease.[15] One of the advantages of screening for infection, rather than treating blindly, is that it allows appropriate management of the male partner, as well as any other contact tracing.

If *C. trachomatis* infection is detected it may be treated with oral doxycycline 100 mg twice daily for seven days or a single dose of azithromycin 1 g. Erythromycin or tetracyclines such as minocycline can also be used. It is mandatory to treat both partners. The same regimes may be used as prophylaxis, but as Macmillan[16] points out, blind use of antibiotics in this way can increase the problem of antibiotic resistance and maintain the bacterial load of chlamydia in the community. It may also prove to be less cost effective than screening.

As well as causing pelvic inflammatory disease, active *C. trachomatis* at the time of embryo transfer can reduce the chances of conception.[17] This may be because unsuspected chlamydial infection induces an inflammatory reaction in the uterus which impairs embryo implantation and/or facilitates immune rejection after transfer. Old chlamydial infection (as confirmed by elevated IgG antibodies), however, has not been found to be associated with a poor IVF outcome if couples are treated with doxycycline before the cycle.[18]

C. trachomatis is not the only organism that can be introduced into the endometrial cavity at embryo transfer. Various studies[19–21] have investigated the nature of bacterial flora found in the cervical canal at the time of the procedure. Several groups have agreed that the presence of certain pathogens is a marker of poor prognostic outcome for IVF, possibly because of the provocation of local endometritis. It is less clear what measures can be taken to eliminate such bacteria and whether they will subsequently improve pregnancy rates.

There have been many organisms identified from endocervical swabs and/or catheters that have been implicated in a reduced chance of pregnancy. These include *Escherichia coli* and *Streptococcus* spp.[19,20] Conversely, certain *Lactobacilli* have been found to have a positive effect on IVF outcome.[20] This positive effect may be due to the *Lactobacillus* inhibiting the growth of potentially virulent bacteria by producing lactic acid and hydrogen peroxide (H_2O_2). Lactic acid helps to maintain a low vaginal pH that is inhibitory to the growth of most microbes. Hydrogen peroxide is also known to kill bacteria.

We found just one published randomised controlled trial[22] studying the implantation rates during IVF cycles according to the use, or not, of antibiotics around the time of embryo transfer. This study found no difference in implantation rates between women who received amoxicillin and clavulanic acid and those who did not. A research group at Guy's and St Thomas' Assisted Conception Unit has recently completed a similar prospective randomised trial examining the role of two doses of co-amoxiclav around the time of embryo transfer (unpublished data). The results concur with the other randomised controlled trial. Such prophylaxis can therefore not be recommended at present.

As some cervical pathogens are known to reduce conception following IVF it seems wise to clean any obvious discharge from the cervix prior to the transfer and to avoid touching the catheter tip on the vaginal walls or external cervix.

Despite its association with first trimester miscarriage and the high prevalence in women having assisted conception,[23] several studies have concurred that bacterial vaginosis has no influence on the pregnancy rate following IVF.[24,25] Liversedge *et al.*[24] conclude that 'routine screening for bacterial vaginosis in the hope of improving the success of IVF treatment is not justified.'

Perhaps one of the main difficulties with using antibiotic prophylaxis for the female partner around the time of TVEC and embryo transfer is that the effect on vaginal flora is unpredictable. Antibacterials may affect not only pathogens but also beneficial commensals and any effect may be short lived.

Some clinicians are reluctant to administer antibiotics during IVF embryo transfer because of concern about embryo toxicity. We have been

Box 1
Main recommendations from this article

- Women should ideally be screened for *C. trachomatis* by PCR or LCR before commencing IVF treatment.
- Where screening has not occurred, embryo transfer should be covered by appropriate antibiotic prophylaxis.
- Scrupulous transvaginal scan probe hygiene should be maintained.
- During egg collection the aspiration needle tip must be kept sterile by a no-touch technique. Endometriomas should be avoided.
- Women at high risk of pelvic infection should be offered broad spectrum antibiotic prophylaxis at egg collection.
- The cervix should be cleansed just before embryo transfer.
- There is insufficient data to support the routine use of antibiotics (other than *C. trachomatis* prophylaxis in the absence of screening) at the time of embryo transfer.

unable to find any studies specifically looking at this, yet there are plenty of studies describing the use of antibiotics, apparently without detriment.

Conclusion

The use of prophylactic antibiotics during IVF embryo transfer remains controversial. Iatrogenic infections resulting from TVEC are rare and there is little evidence that pelvic infection is prevented by the routine use of antibiotic prophylaxis. The role of low grade endometrial infections provoked by embryo transfer on implantation/pregnancy rates is less clear and we would like to see more studies examining the role of different antibiotic regimes around the time of transfer. **Box 1** highlights general recommendations to reduce the risk of infection provoked by IVF treatment.

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