Hum Fertil (Camb). Author manuscript; available in PMC 2011 April 01.

Published in final edited form as:
Hum Fertil (Camb). 2010 September ; 13(3): 115–125. doi:10.3109/14647273.2010.513893.

Impact of *Chlamydia trachomatis* in the reproductive setting: British Fertility Society Guidelines for Practice

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Abstract

C. trachomatis infection of the genital tract is the most common sexually transmitted infection and has a worldwide distribution. The consequences of infection have an adverse effect on the reproductive health of women and are a common cause of infertility. Recent evidence also suggests an adverse effect on male reproduction. There is a need to standardise the approach to managing the impact of *C. trachomatis* infection on reproductive health. We have surveyed current UK practice towards screening and management of *Chlamydia* infections in the fertility setting. We found that at least 90% of clinicians surveyed offered screening. The literature on this topic was examined and revealed a paucity of solid evidence for estimating the risks of long-term reproductive sequelae following lower genital tract infection with *C. trachomatis*. The mechanism for the damage that occurs following Chlamydial infections is uncertain. However, instrumentation of the uterus in women with *C. trachomatis* infection is associated with a high risk of pelvic inflammatory disease, which can be prevented by appropriate antibiotic treatment andmay prevent infected women from being at increased risk of the adverse sequelae such as ectopic pregnancy and tubal factor infertility. Recommendations for practice have been proposed and the need for further studies identified.

Keywords

Chlamydia; screening; infertility; serology; NAAT; guideline; BFS

Introduction

C. trachomatis, an obligate intracellular bacterium, is one of the most common sexually transmitted infections with 89 million new cases thought to occur globally per annum(Adams et al., 2004; Manavi, 2006; Bébéar & de Barbeyrac, 2009). In Europe, the reported incidence of Chlamydial infections has increased in the past ten years, some of whichmay be accounted for through increased testing and the availability of more sensitive

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tests, but may also reflect an increase in risk-taking behaviour. In 2006, there were 112,473 *C. trachomatis* diagnoses identified from laboratory reports in England and Wales and 17,962 from Scotland (Health Protection Agency, 2007).

C. trachomatis infection is =common in those under 25 yrs, with rates decreasing thereafter (Holmes et al., 1999; Horner and Boag, 2006). One in 14 young people (<25yrs old) screened outside departments of Genitourinary Medicine as part of the National *Chlamydia* Screening Programme in England were *Chlamydia*-positive (National Chlamydia Screening Programme, 2009). This probably represents selective testing of higher risk individuals as population based studies have observed prevalences in the range 2-6% with a higher prevalence in women aged 16-19 and men 20-24 (Fenton et al., 2001; Macleod et al., 2005).

There are some studies of *C. trachomatis in* men and women undergoing investigations for infertility using modern screening methods. The *C. trachomatis* positivity rate is about 2-5 % in men and women and may be as low as 1% or as high as 13% among couples (Bezold et al., 2007; Eggert-Kruse et al., 1997; Idahl et al., 2004; Imudia et al., 2008; Samra et al., 1994) as only one partner of a couple may test positive (Clad et al., 2001; Idahl et al., 2004). Current infection does not necessarily mean recent infection, as the infection can persist for many years in the absence of treatment (Molano et al., 2005). The major sequelae of *C. trachomatis* infection in women are tubal factor infertility and tubal ectopic pregnancy. Sequelae of *C. trachomatis* infection in men may include male factor infertility but why this occurs remains uncertain (Joki-Korpela et al., 2009).

Annual NHS costs due to *C. trachomatis* infection and its purported complications are estimated at above £100 million (Department of Health, 2004). In 2007, due to concern about the public health impact of *C. trachomatis* infection, the National *Chlamydia* Screening Programme (National Chlamydia Screening Programme, 2009) was introduced in England offering screening to anyone under 25 (http://www.Chlamydiascreening.nhs.uk). However, in Scotland no such programme has been introduced. The Scottish Intercollegiate Guidelines Network (2009) state that '*in the absence of a complication rate of 10% or more in women with untreated Chlamydial infection, there is no evidence that a screening programme is cost effective with regard to reducing morbidity*'. Furthermore, the National Collaborating Centre for Women's and Children's Health (2008) recommended that *chlamydia* screening should not be offered to pregnant women, based on the evidence supporting the NICE Routine Antenatal Care Guideline.

With regard to infertility patients receiving treatments such as IVF, the Royal College of Gynaecologists (1998) recommended that women should be screened for *C. trachomatis*, or given appropriate antibiotic prophylaxis, before any uterine instrumentation takes place. This was reiterated in the later NICE guidelines (National Collaborating Centre for Women's and Children's Health, 2004). However, Sowerby and Parsons (2004) noted that 53% of UK clinics either screen the female partner or give appropriate antibiotic prophylaxis. In the recruitment of sperm, egg and embryo donors the most recent UK guidelines produced by the Association of Biomedical Andrologists, Association of Clinical Embryologists, British Andrology Society, British Fertility Society and Royal College of Obstetricians Gynaecologists (2008) recommend that all donors be screened for *C. trachomatis* prior to donation, and this is reiterated in the 8th Edition of the HFEA Code of Practice (HFEA, 2009).

Aims

1. To survey current practice in relation to *C. trachomatis* screening and treatment

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2. To produce evidence-based guidelines to help UK fertility clinics in their practice of screening and managing couples with possible *C. trachomatis* infection.

Materials and methods

A questionnaire was developed examining key questions relating to the practice of *chlamydia* screening and management. The questionnaire was sent to the Person Responsible in all HFEA Licensed Clinics and to all practicing consultant gynaecologists registered with the Royal College of Obstetricians and Gynaecologists. There were separate questionnaires for private and NHS services. Where both NHS and private patients were treated they were requested to fill in both questionnaires in order to distinguish any differences.

Questions were asked in relation to whether patients were offered screening, the type of screening offered (e.g. swabs, serology), type of treatment given if positive. Statistical analysis was undertaken using the Chi square test.

Results

A total of 1253 questionnaire were sent out; a follow up request was not sent to those that did not respond. In total 220 responses were received giving a16% response rate, Table 1 summarises the main findings. Of the responses received, 91 stated that they provide private services and 181, NHS services. Of the centres that responded to the question on why they undertook serology, 16 of 72 (22.2%) indicated they did so to assess the risk of current infection (data not shown). Less than 18% of the centres surveyed used *Chlamydia* serology routinely and most centres did not use it selectively either. Over 70% of centres were not sure which assay was used to test for *chlamydial* antibodies (Table 1).

Discussion of survey findings

As only 16% of individuals surveyed responded we are limited in our ability to assert that the findings are representative of practice in the UK. Nonetheless, the results suggest that the majority of patients are screened for *C. trachomatis* though many centres apply a selective approach and do not screen all patients. Thus, it is plausible that most centres are currently compliant with the NICE recommendations; in contrast to a survey undertaken 5 years ago (Sowerby & Parson 2004). It is notable that of those not offering screening, it was higher in the private sector though not statistically significantly so. It may be that these were patients undergoing specific treatment such as IVF or they may previously have been investigated in an NHS setting. It is however, not possible to be certain as to why s this question was not asked.

It is significant that several centres were uncertain which serological assay was used because interpretation of serology results is dependent on the test used. Furthermore, the finding of serology being used for assessing current infection in a fifth of centres that did the test, suggests that it is often used for the wrong reasons. This indicates further training is required by many centres in the use of *Chlamydia* serology.

Scope

The remainder of this paper reviews the current literature systematically in order to provide evidence based guidance in the following areas:

- *C. trachomatis* infection and adverse reproductive outcome
- Screening for *C. trachomatis* in infertile women

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- Screening for tubal damage using *chlamydial* antibody testing (serology).
- Male infertility and *C. trachomatis*
- Diagnosis and detection of chlamydial infection using Nucleic Acid Amplification Tests.
- Detection of current chlamydial infection using serology
- Treatment of patients diagnosed with chlamydial infection
- Prophylactic antibiotic use
- Counselling and guidance in the event of a positive result.
- Contact tracing for patients recognised as having current infection
- Counselling in the infertility setting
- Mode of obtaining result of *chlamydia* screening
- Storage of gametes and embryos

C. trachomatis infection and adverse reproductive outcome

There is good evidence that many individuals infected with C. *trachomatis* become micro-organism detection negative with time (Quine et al., 1996; Molano et al., 2005). Women usually present many years after they were at greatest risk of having an infective episode. Thus tests which only detect the presence of the micro-organism, such as nucleic acid amplification tests (NAATs) cannot be used to assess previous exposure to *C. trachomatis*. Serology, a measure of past exposure to chlamydial infection, has been measured in case control studies of women with infertility (Land et al., 1998). Its usefulness lies in being able to detect women who have previously been exposed to *chlamydia* infection,and identified as being at high risk of tubal damage (Akande, 2002). However, studies adopting this approach have been criticised because of poor assay sensitivity and specificity, there having been no rigorous evaluation against large numbers of well-defined antibody positive and negative control sera.

In the absence of treatment, women infected with *C. trachomatis* may develop pelvic inflammatory disease (PID) which can result in tubal factor infertility (TFI), ectopic pregnancy (EP) and chronic pelvic pain (Westrom et al., 1992; Paavonen & Eggert-Kruse, 1999; Hu et al., 2004; Simms & Horner, 2008). However, this familiar phrase in the world of chlamydial research belies a fundamental problem; uncertainty about how many cases of genital *C. trachomatis* infection go on to develop PID and its associated sequelae (Wallace et al., 2008).

Instrumentation of the uterus in women with *C. trachomatis* infection is associated with a high risk (>50%) of developing pelvic inflammatory disease following termination of pregnancy (Blackwell et al., 1993). A trial comparing screening of *C. trachomatis* versus non screening, prior to termination of pregnancy demonstrated a significant reduction in post abortion pelvic inflammatory disease at 4 weeks in those screened and treated if positive (Giertz et al., 1987). There is also strong evidence to suggest that women with confirmed pelvic inflammatory disease are at increased risk of ectopic pregnancy, tubal factor infertility and chronic pelvic pain (Weström et al., 1992).

Difficulties in determining the effect of female genital *C. trachomatis* infection on adverse reproductive outcome stem from not only the design of the studies, but from the lack of a reliable method for measuring a history of PID. Much of the current assumptions on risk of subsequent infertility are based on retrospective case-control studies (Walters et al., 1988;

Chrysostomou et al., 1992; Weström et al., 1992; Odland et al., 1993; Van Valkengoed et al., 2004; Low et al., 2006; Bakken et al., 2007; Bjartling et al., 2007; and Machado et al., 2007). Many of these studies have been performed on populations where infertility was at the extremes of the distribution i.e., extremely common or rare, or used data that did not account for misdiagnoses, and there is considerable error in their estimates of risk ratios (Van Valkengoed et al., 2004; Bakken, 2008; Garnett, 2008). Moreover, retrospective and prospective case control studies on infertility are prone to confounding variables that have not always been accounted for, such as the effect of other sexually transmitted infections (e.g. *Neisseria gonorrhoea* and syphilis).

The mechanism by which *C. trachomatis* infection accounts for adhesions, tubal damage or occlusion in humans, leading to female infertility is unclear. It is believed to be primarily immunologically mediated and not a direct consequence of destruction of tissue by the organism (Rice & Schacter, 1991; Beatty et al., 1994), although more recent evidence does support a direct cytotoxic effect of *C. trachomatis* on the ciliated epithelium (Baczynska et al., 2007). There are experimental animal models (mainly in rodent species) of genital Chlamydial infection that provide clues to disease pathogenesis. However, these experimental infections are usually conducted using defined infectious doses under highly controlled conditions for relatively short periods in animals that have limited genetic variability and different immune evasion strategies than in man (Brunham & Rey-Ladino, 2005). Consequently, care needs to be taken when interpreting the data for the pathogenesis of human Chlamydial infections where all of the above factors vary greatly. It is thought that lower genital tract *C. trachomatis* infection ascends to the upper reproductive tract resulting in salpingitis, and it has been proposed that an antibody response to the Chlamydial heat shock protein (hsp-60) may cause a tubal inflammatory response leading to tubal blockage or a predisposition to tubal implantation (Ault et al., 1998; Bjartling et al., 2007). Repeated infections with *C. trachomatis* are also thought to increase tubal damage (Hillis et al., 1997; Westrom et al.,1992; Rank et al., 1995).

Recommendation—There is an association between *C. trachomatis* infection and adverse reproductive sequelae in women; efforts should therefore be made to prevent infection.

Screening for *C. trachomatis* in infertile women

Due to the silent nature of *C. trachomatis* infection, most infected women are asymptomatic and therefore go unrecognised and untreated. Although the prevalence of *C. trachomatis* among subfertile women in the UK is only 1.9% (MacMillan & Templeton 1999), uterine instrumentation carried out routinely as part of the infertility investigation may reactivate or introduce upper tract dissemination of endocervical *C. trachomatis* infection, resulting in iatrogenic pelvic inflammatory disease. Clinical pelvic infection following hysterosalpingography (HSG) has been reported in up to 4% of cases and in 10% of patients with tubal disease (Forsey et al., 1990). Prophylactic antibiotics are effective in reducing this condition and should be considered (National Collaborating Centre for Women's & Children's Health, 2004). There is evidence that screening for, and treating cervical *C. trachomatis* can reduce the incidence of pelvic inflammatory disease in women at increased risk of this infection. The Chief Medical Officer's Expert Advisory Group on *Chlamydia* has called for action to reduce the prevalence and morbidity of Chlamydial infection. It recommends that consideration be given to screening couples attending fertility clinics and women undergoing procedures requiring instrumentation of the uterus.

Recommendation—Before undergoing uterine instrumentation women should be offered screening for *C. trachomatis*. Prophylactic antibiotics should be considered before uterine instrumentation if screening has not been carried out.

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Screening for tubal damage using *Chlamydia* antibody testing (serology)

Laparoscopy is currently recognised as the gold standard for diagnosing tubal infertility, though other methods such as Hystero Contrast Sonography and Hysterosalpingograpy exist. Infection with *C. trachomatis* results in the formation of antibodies detectable in the serum. Studies using laparoscopy confirm that serological evidence of past infection with *C. trachomatis* is associated with a significantly increased risk of women suffering tubal infertility (Akande et al., 2003; Coppus et al., 2007). Furthermore, the severity of tubal damage found in infertile women is directly related to serum antibody titre levels (Akande, 2003).

Because there are justified constraints to the indiscriminate use of laparoscopy and other invasive diagnostic tests, there is a need to minimise the number of patients who do not have tubal damage who are subjected to these investigations. Screening is defined as a procedure that helps identify a specified disease or condition (in this context tubal damage). Most screened individuals will be unaffected. A meta-analysis (Mol et al., 1997) showed that the performance of *Chlamydia* antibody testing on detecting tubal damage depended on the assay used, and found the WIF test with the ELISA and MIF test to be superior to the immuno-peroxidase assay.

Clinical judgment and not a statistical calculation are often required to decide what test to use. For example in screening for lethal disease (e.g. HIV), high sensitivity is desirable though the trade off is usually lower specificity. However, when dealing with a non life-threatening condition such as tubal damage, a high cut off (lower sensitivity) may be chosen which may miss some cases but lead to fewer women who do not have the disease being subjected to invasive and costly laparoscopy (high specificity).

Recommendation—Serology is non-invasive and may be used as a screening test to detect evidence of past chlamydial infection. This may help identify women at high risk of having tubal damage as a cause of their infertility.

Male infertility and *C. trachomatis*

There have been a number of studies on the relationship between *C. trachomatis* infection and sperm quality, with conflicting results. However, as for the studies in women (above), there have been major differences in study design with: (a) significant variation in the methodology used to measuring the history of chlamydial infection (i.e. serology versus molecular methods); as well as (b) variable and sometimes inadequate methods to assess semen quality (see Pacey and Eley, 2004 for review). More recent studies (Hosseinzadeh et al., 2004; Bezold et al., 2007; Al-Mously et al., 2009), using molecular methods to detect infection, and robust methods of laboratory andrology to examine semen, have generally found that men with a current infection of *C. trachomatis* have poorer quality ejaculates compared than men who do not. It is unclear whether this is because of reduced levels of spermatogenesis in the presence of the bacterium, or whether infection causes an altered ejaculatory response. However, it has been observed that persistent infection can result in the scarring of ejaculatory ducts or loss of stereocilia (Gonzalez-Jiminez & Villanueva-Dmaz, 2006).

In addition to any changes in semen quality, there is growing evidence to suggest that exposure to *C. trachomatis* can affect sperm function (Pacey and Eley, 2004; Eley et al., 2005b). *In vitro* experiments have shown that *C. trachomatis* triggers tyrosine phosphorylation of sperm proteins (Hosseinzadeh et al., 2000), induces premature sperm death (Hosseinzadeh et al., 2001) and stimulates an apoptosis-like response in sperm (Eley et al., 2005a; Satta et al., 2006), leading to increased levels of sperm DNA fragmentation

(Satta et al., 2006; Gallegos et al., 2008). At least some of these effects are caused by lipopolysaccharides. (Hosseinzadeh et al., 2003).

Recommendation—Some evidence indicates that *C. trachomatis* infection can affect sperm quality and sperm function. However it has not been shown that empirical treatment improves reproductive outcome in males.

Diagnosis and detection of *C. trachomatis* infection using Nucleic Acid Amplification Tests

NAATs are now the test of choice for detecting current *C. trachomatis* infection (Horner & Boag, 2006). These tests have a high sensitivity (>90%) and specificity (>99.5%) for detecting the micro-organism. Although no single test provides 100% sensitivity and specificity, NAATs are the most accurate tests on the market. Four commercial assays are currently available for routine use and it is anticipated that this number will increase.

However, it can be demonstrated i*n vitro* that *C. trachomatis* can enter a latent state under stressful conditions such as exposure to interferon gamma (IFN-γ) (an important cytokine involved in cell mediated immunity), exposure to penicillins (Hogan et al., 2004) or amino acid starvation. This state allows *C. trachomatis* to remain dormant but, on removing the stressful conditions, the bacteria can subsequently be recovered from culture. This may be an adaptive survival mechanism *in vivo* (Hogan et al., 2004) and it has been proposed that women with tubal disease who are *Chlamydia*-antibody positive, in particular with the IgA antibody, are at risk of having persistent latent infection (Patton et al., 1994; Witkin & Linhares, 2002).

In men a first voided urine specimen is the test of choice and is just as accurate as a urethral swab, which can be painful. In women although a cervical specimen is to be preferred there is increasing evidence that a vulvo-vaginal specimen is just as accurate (Horner & Boag, 2006). Although first voided urine specimens are licensed in women, studies indicate a wide variation in sensitivity suggesting it may not be as reliable in some hands (Horner & Boag, 2006). This probably reflects the lower Chlamydial load in this specimen type compared to cervical and vulvo-vaginal specimens (Michel, 2007; Wiggins, 2009).

It is important that care is taken, and local guidelines are followed, when obtaining and transporting these specimens, as poor quality specimens may result in reduced sensitivity. To avoid contamination (Horner & Boag, 2006) men and women should have held their urine for 2 hours (minimum one hour) and when taking a vulvo-vaginal or cervical swab it should be rotated for at least 15 seconds.

Recommendation—Although no single test provides 100% sensitivity and specificity, NAATs are the most accurate tests on the market. For women this should either be a cervical or vulvo-vaginal specimen.

Detection of current Chlamydial infection using serology

Serology assays to detect *C. trachomatis* antibodies in exposed patients are liable to cross-reaction with sera from patients exposed to other chlamydial species, particularly *C. pneumoniae* (Johnson & Horner, 2008), a common respiratory pathogen with which it shares genetic homology (Kalman et al., (1999). Chlamydial antigens, such as the 60kDa heat shock protein (hsp60) and lipopolysaccharide, cross-react with other bacterial species (Newhall et al., 1982; Kalman et al., 1999; Sanchez-Campillo et al., 1999). The microimmunofluorescence (MIF) assay, which detects antibodies to Chlamydial elementary bodies, has long been considered to be the ‘gold standard’ for serodiagnosis of *C. trachomatis* (Persson, 2002; Johnson & Horner, 2008). However, the procedure lacks

standardisation, is subjective, not designed for high-throughput use and its specificity is compromised by cross-reactivity with other Chlamydial species (Persson, 2002; Johnson & Horner, 2008). The highly immunogenic major outer membrane protein (MOMP) making up 60% of the total outer membrane protein (Caldwell et al., 1981), is the basis of several commercially produced ELISAs using *C. trachomatis* specific peptides (Johnson & Horner, 2008). However, although specificity is high; >95% in women, sensitivity is <60% and that in men, lower still ~40% (Wills et al., 2009). There is currently no evidence supporting the use of Chlamydial serology for detecting persistent hidden (NAAT negative) infection which may be at risk of reactivating (Dietrich et al., 2008). A positive *chlamydial* serology test should be viewed with caution in attributing causality because of problems with sensitivity and specificity.

Recommendation—*Chlamydial* antibody testing (serology) is not useful in detecting current infection.

Treatment of patients diagnosed with *C. trachomatis* infection

Azithromycin 1g and doxycycline 100mgs bd for 7 days have been shown to be >95% effective in the treatment of uncomplicated lower genital tract *C. trachomatis* infection. (Horner and Boag, 2006; Horner, 2008). For those with upper genital tract disease i.e., pelvic inflammatory disease, a prolonged course of treatment for up to 14 days is recommended (Royal College of Obstetricians and Gynaecologists, 2008).

Recommendation—*C. trachomatis* detection-positive patients should be assessed for the presence of upper genital tract disease and if present treated according to RCOG guidelines. Patients with uncomplicated disease should be treated with: Azithromycin 1g or Doxycycline 100mgs bd for seven days.

Prophylactic antibiotic use

There is no evidence to support the use of prophylactic antibiotics in women who are NAAT-negative and *chlamydia*-antibody positive. However further studies are merited as the potential for persistent infection in antibody-positive women in the presence of a negative lower genital tract NAAT cannot definitely be excluded as the evidence is inconsistent. A randomised controlled trial of prophylactic antibiotics in *Chlamydia*-antibody women (using new *C. trachomatis* specific MOMP peptide assays) who are NAAT negative is required.

Recommendation—Those women who are NAAT-positive for *C. trachomatis* or are contacts of partners who are *C. trachomatis* NAAT-positive should be treated.

Counselling and guidance in the event of a positive test result

C. trachomatis infection remains a stigma for many and testing can be a sensitive issue. This section highlights the patient's need for information, the importance of support for patients receiving a positive result and the need for guidance in providing advice (Table 2). Whilst general practitioners undertake the vast majority of screening for sexually transmitted diseases (STIs) (Temple-Smith et al., 1999; McNulty et al., 2004), specialist (tertiary) services have a valuable role in meeting these needs In some cases, patients may seek a private referral.

It should also be remembered that *C. trachomatis* infection can persist for years in some individuals (Molano et al., 2005) while their regular partner may not test positive (Quinn et al., 1996; Clad et al., 2001). Thus the detection of *C. trachomatis* does not necessarily mean recent acquisition from another partner. Table 2 provides a framework for counselling a

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patient who is found to be positive for *C. trachomatis* based on the Bristish Association for Sexual Health and HIV guidelines.

Recommendation—Health professionals offering *Chlamydia* screening should be trained to inform individuals of the potential effects of positive screening.

Contact tracing for patients recognised as having current infection

Partner notification for sexually transmitted infections such as *C. trachomatis* is essential to prevent re-infection of the patient, sequelae in untreated partners and onward transmission. Patients diagnosed with *C. trachomatis* should be advised to inform partners at risk and/or be referred to Genitourinary Medicine (GUM) for management and support, with partner notification. This can be undertaken successfully outside GUM departments by nurses with minimal training and on-going support from a health adviser (Low et al., 2006; Horner & Boag, 2006). Health advisers usually work in GUM departments and specialise in partner notification.

National guidelines recommend that all sexual contacts within the past six months should be offered treatment and anti-Chlamydial therapy (Horner & Boag, 2006). Partners should not be directly informed by the service without the consent of the patient who has tested positive.

Partners may be managed by the Infertility Clinic, or referred to GUM where treatment is free and confidential. Some partners may prefer to attend their GP. Partners should be offered testing and treatment without delay, to reduce the risk of patient re-infection. Treatment of partners should be given on the day the test is taken, without waiting for the result. Partners who have recently tested negative should still be offered treatment.

Patients who are unwilling to notify their partners themselves should be referred to a GUM clinic for assistance from a Health Adviser who will inform the partner confidentially, without mentioning the patient's name. Patients who test negative but report a history of treatment for *C. trachomatis* during their current relationship should be asked to confirm that their partner was treated at the same time.

Recommendation—Partner notification following *C. trachomatis* infection is advisable to prevent re-infection of the patient, sequelae in untreated partners and onward transmission.

Counselling in the infertility setting

The main focus of counselling in this setting is to inform the patient of the association of a positive Chlamydial result with tubal infertility and ectopic pregnancy. Patients need to be comfortable and informed before consenting to screening; accurate information which can normalise and subsequently de-stigmatise infection must be available; and feelings of embarrassment should be addressed in a sympathetic manner. The very real concerns that exist for patients regarding stigma, informing partners, confidentiality, physically being screened, and, in particular, future reproductive health, make a positive diagnosis more difficult to cope with.

Screening for *C. trachomatis* often evokes anxiety through the realisation that there is a possibility of being infected. In one study, the verbal and written information provided to patients led to most recalling the possibility of infertility after infection (Duncan et al., ; 2001). This provoked a mixed reaction; relief that infection was diagnosed but anxiety about future reproductive morbidity.

Recommendation—Patients should be informed of the potential association between *C. trachomatis* infection and adverse reproductive outcome.

Mode of obtaining result of *C. trachomatis* screening

Waiting for the result of screening causes concern about the implications of a potential positive diagnosis and collecting the result in itself can be the cause of much anxiety. The method of obtaining the result is important, as some methods will be seen as risking confidentiality, unsupportive or potentially increasing anxiety (Dixon-Woods et al., 2001). Some patients prefer to be in control by being able to telephone for their results, whilst others will prefer a second appointment, to allow time to absorb the information and ask questions; others may prefer to receive the result by post. It is recommended that units develop adequate policies for providing some or all of these options.

Recommendation—Patients should be offered the opportunity to choose how they receive the result of their Chlamydia test.

Storage of gametes and embryos

Since it is known *C. trachomatis* can survive in liquid nitrogen (Sherman & Jordan, 1985) and that infection following insemination with cryopreserved donor semen is possible (Broder *et al.*, 2007), the freezing and storage of gametes and embryos from patients with an active *C. trachomatis* infection is of obvious concern. This is not only to prevent women who receive treatment with thawed gametes and embryos from becoming infected with *C. trachomatis*, but because of the theoretical concern that the bacteria may cross-contaminate other (C. *trachomatis* negative) samples being stored in the same cryostorage vessel.

To date, such cross contamination has only been shown with regard to Hepatitis B during storage of peripheral blood stem cells (Tedder et al., 1995) and has never been demonstrated during reproductive tissue storage. However, the HFEA now require that all patients placing material in storage be screened for bloodborne viruses prior to placing material in storage (Human Fertilisation and Embryology Authority, 2009). For patients undergoing planned IVF treatment, a similar level of risk reduction will be achieved if both partners are screened and treated for *C. trachomatis*.

Recommendation—All patients should be screened for *C. trachomatis* prior to placing gametes or embryos in storage. Where embryos are created, the gamete providers should be screened, and if positive treated.

However, this may not be possible for men banking sperm prior to cancer therapy, as there is often insufficient time between diagnosis and the start of treatment to allow *C. trachomatis* testing and treatment (Tomlinson and Pacey, 2003). In such cases, men who are *C. trachomatis* positive should be advised at the time of storage about the risks to future partners of acquiring an infection and this should be reiterated at the time of any future treatment.

Recommendation—Where screening is not possible, the gamete provider and their partner should be told of the risks of infection of using unscreened material in treatment.

The risk of *C. trachomatis* negative samples being contaminated with bacteria from positive (unscreened material) will vary according to the type of storage systems used (see Tomlinson, 2009). Whilst sperm washing before freezing could theoretically help to reduce the bacterial load in *C. trachomatis* positive samples, this remains unproven and

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experimental data suggest that sperm washing is only partially effective in removing the bacteria from men with an active infection (Al-Mously et al., 2009).

Recommendation—Laboratory staff should carry out a risk assessment of their storage system to reduce the likelihood of cross-contamination with Chlamydia during storage.

Conclusion

There is a paucity of solid evidence for estimating the risks of long-term reproductive sequelae following lower genital tract infection with *C. trachomatis*. Nevertheless instrumentation of the uterus in women with *C. trachomatis* is associated with a high risk of pelvic inflammatory disease, which can be prevented by treatment. There is good evidence that women with pelvic inflammatory disease are at increased risk of ectopic pregnancy and tubal factor infertility.

There is a need for:

1. Well-designed prospective female and male patient cohort studies on clearly defined adverse reproductive outcomes, such as tubal ectopic pregnancy and semen quality. Quantifying risk is fundamentally important as women and men diagnosed with apparently uncomplicated *C. trachomatis* infection need to be given reliable , evidence-based information on their subsequent risk of infertility.
2. Randomised controlled treatment trials of *chlamydia* antibody-positive NAAT negative women undergoing investigation for infertility.
3. Randomised controlled trials to investigate whether semen quality and sperm function is improved following empirical treatment for *C. trachomatis*.

Acknowledgments

1The authors gratefully acknowledge the expertise of Professor Gary Entrican (Moredun Research Institute, Edinburgh), Professor Sarah Howie (University of Edinburgh) and Dr Sharon Cameron (Royal Infirmary of Edinburgh) in the preparation of this document.

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Table 1

Findings of survey in relation to clinic practice for private and NHS patients		NHS (n=181)	
Private (n=91)			
Screening offered in clinic	82 (90.1%)	174 (96.2%)	**NS**
Screening offered to all patients	**47 (51.6%)**	**97 (53.6%)**	
Genital swab used as screening method	**75 (82.4%)**	**151 (83.4%)**	**NS**
Type of treatment used if positive			
Doxyxlycline	**85 (47.0%)**	**42 (46.2%)**	**NS**
Azithromycin	**72 (39.8%)**	**35 (38.5%)**	**NS**
Serology always used	**16 (17.6%)**	**25 (13.8%)**	**NS**
Never used	**61 (67.0%)**	**122 (67.4%)**	**NS**
Not sure of what type of serology	**66 (72.5%)**	**136 (75.1%)**	**NS**

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Table 2

The following may be used as guidance for counselling a patient with *Chlamydia* infection

1. What is *C.trachomatis* and how it is transmitted
a. It is a common infection in sexually active individuals
b. It is primarily sexually transmitted, but may not be always so
c. If asymptomatic there is evidence that it could have persisted for months or years
2. The diagnosis of *C.trachomatis*:
a. It is often asymptomatic in both men and women
b. Whilst tests are accurate, no test is absolutely so
3. The complications of untreated *C.trachomatis*
4. Side effects and importance of complying fully with treatment and what to do if a dose is missed.
5. The importance of their sexual partner(s) being evaluated and treated.
6. Advised to abstain from sexual intercourse until they and their partner(s) have completed therapy (and waited seven days if treated with azithromycin).