Serological Screening for Chlamydia in Tubal Factor Subfertility

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Chlamydia is the most common sexually transmitted infection in industrialized and under developed countries. Usually these infections remain asymptomatic and may lead to tubal factor subfertility. An association has been noticed between Chlamydia IgG antibodies and tubal factor subfertility. This non-invasive screening test is now being used in fertility workups for tubal factor subfertility. The tests that are currently being used for subfertility workup are hysterosalpingography (HSG), laparoscopy and dye hydro-tubation. Hysterosalpingo-contrast-sonography and hysteroscopy are expensive and invasive techniques. Chlamydia antibody tests are of predictive value in the detection of tubal pathology and are quantitatively related to the severity of damage. For practical clinical purposes Chlamydia serology is useful mainly as a screening test for the likelihood of tubal damage in infertile women and may facilitate in decision making regarding selecting women to undergo expensive laparoscopy.

Chlamydia

Chlamydia are obligate intracellular parasites containing both DNA and RNA.1 The genus Chlamydiaceae consists of nine species, out of which C. trachomatis, C. pneumonia and C. psittaci are the most common human pathogens. Chlamydia trachomatis is predominately a human pathogen and is a major cause of sexually transmitted infection (STI). C. trachomatis has been sub-divided into two biovars: trachoma (causing ocular disease, genital infections and infant pneumonias) and lymphogranuloma venereum (LGV). The trachoma biovars is further sub-divided into 15 serotypes on the basis of antigenic differences in their cell walls. The antigenicity of the Chlamydia cell wall is determined by the outer membrane, which consists of a lipopolysaccharides (LPS) and proteins, including the major outer membrane protein (MOMP). LPS is a common component of the outer membrane of all Chlamydiaceae. MOMP has epitopes which are not only species but can be used to identify different serotypes as well.2,17.

Genital infections caused by C. trachomatis are the most common bacterial sexually transmitted diseases (STD) in the United States. More than 4 million cases occur each year and the annual cost is too high.3 According to the Centre for Disease Control and Prevention age is the sociodemographic factor most strongly associated with C. trachomatis.2 The prevalence of Chlamydia in sexually active adolescent females is greater than 10%. Other factors associated with higher prevalence include living in urban areas, black race, and lower socioeconomic status.2 A study was carried out for local prevalence rates for STIs in Faisalabad, Pakistan. Syphilis was present in 29.5% of patients (n=452); gonorrhea, in 13% (n=200), HSV-2, in 3.2% (n=49), chlamydia, in 4.7% (n=72) and chancroid, in 1.3% (n=20).4 The overall prevalence of Chlamydia in US regardless of region is at least 5%.2 Infection caused by chlamydia is usually asymptomatic (70-80%) and carriers are usually common; they contribute to widespread prevalence of chlamydia and its long term sequelae: tubal infertility (6-21%), including ectopic pregnancy (17-9%), pelvic inflammatory disease, chronic pelvic pain (18-24%) and development of cervical cancer.5,6,14.

Tubal factor subfertility

Sub-fertility is a worldwide health problem with one in six couples suffering from this condition and with a major economic burden on the global healthcare industry. Estimates of global infertility rates suggest that 15% of couples are subfertile defined as: Failure to conceive after one year of unprotected sexual intercourse.

Tubal factor infertility is among the leading causes of female factor infertility accounting for 7-9.8% of all female factor infertility. Tubal disease directly causes from 36-85% of all cases of tubal factor infertility in developed, developing nations respectively and is associated with polymicrobial aetiologies.8 Infection related damage to fallopian tubes caused by Chlamydia trachomatis accounts for more than 70% of cases of infertility in women from developing nations such as sub-Saharan Africa11. Normal tubal function should permit gamete transport, fertilization and the subsequent passage of embryo to the uterus such that implantation can take place at the appropriate stage in the menstrual cycle.

Studies have indicated that the incidence of tubal factor subfertility is approximately 10% after one episode of
infection, about 20% after 2 episodes and >40% after 3 episodes. Some studies show relationship between chlamydia infection and tubal factor subfertility.

**Diagnostic work-up**

Hysterosalpingography (HSG), laparoscopy and dye hydrotubation, hysterosalpingo contrast sonography and hysteroscopy are widely used tests for diagnostic work-up for tubal factor subfertility. These tests are expensive and invasive tests. A meta-analysis evaluating HSG assessment of tubal patency using laparoscopy as gold standard showed 65% sensitivity and 83% specificity. One can deduce from this that HSG is of limited value in detecting tubal damage because of its low sensitivity, its high specificity makes it a better test for identification of tubal patency. The negative predictive value 94% of test as a predictor of tubal patency is also high, suggesting that the normal tubes on HSG is likely to be correct. However its low predictive value (38%) suggests that the test is not reliable indicator of tubal occlusion, it would be wise to use laparoscopic assessment to confirm or refute the findings. But clinical infections after HSG are reported to be 4%.

**Chlamydia antibody testing (CAT) in serum**

HSG has low sensitivity and gold standard laparoscopy is invasive and expensive test which is unsuitable for screening at large scale. Clinicians have searched for other tests that may help in estimating risk of tubal pathology in sub-fertile women. Chlamydia antibody testing (CAT) by microimmunofluorescence tests has been introduced in patients presenting with subfertility. It is simple and inexpensive screening for tubal pathology. More than 70% of women with tubal occlusion have elevated anti-chlamydial antibodies. Humoral immune response to C. trachomatis occurs in humans and persistent antibody levels appear to be most directly correlated with more severe and long standing disease and with reinfection. There is a close correlation between the presence of anti-chlamydial antibodies in females and tubal factor infertility; the closest associations have been found for antibodies against chlamydial heat shock proteins.

Now problem arises in clinical significance of CAT by patients presenting with positive antibodies but without tubal pathology. False positive results leads to increased health care burden due to increased number of laparoscopies done for false positive results. A false negative result with positive tubal pathology is another entity that usually face while dealing with these patients. Therefore, if CAT is used to screen patients for laparoscopies then the number of false positive CAT results should be minimized. A widely used test for Chlamydia is the micro-immunofluorescence (MIF) test which has been considered as gold standard in serological diagnosis of Chlamydia infection. Initially antigens from elementary bodies of each of the serotype of Chlamydia trachomatis were included in the MIF test which provided serotype specific antibody testing. Later for practical reasons number of antigens has been reduced by pooling antigens of epidemiologically related serotypes or by using one broadly reacting serotype, usually L2. However in modified MIF test cross reactivity between C. trachomatis and C. pneumonia occurs. To overcome this problem species specific MIF test has been developed, in which LPS is subtracted which is a common component of outer membrane of all Chlamydiaeae. Land et al studied the role of C. pneumoniae antibodies, as a cause for false positive CAT results. In 240 sub fertile women serological data were compared to laparoscopy findings. The prevalence of C. pneumoniae antibodies using enzyme-linked immunosorbent assay (ELISA) was 75% and did not differ between patients with and without tubal pathology. C. pneumonia antibodies were found in 87% of C. trachomatis positive MIF test and in 66% with a negative MIF test (p<0.0005). Using ELISA instead of MIF for the detection of C. trachomatis antibodies, C. pneumonia antibodies were found in 87% of C. trachomatis positive women, and in 69% of C. trachomatis negative women (p<0.0005). Therefore it was suggested that C. pneumonia antibodies may be the cause of false positive CAT results. Remarkably, tubal pathology was more common in patients that had antibodies to both C. trachomatis and C. Pneumoniae.

Disadvantages of MIF tests are that they are labour intensive, their reading require is observer dependent and inter laboratory variation is significant. To overcome these drawbacks enzyme linked immunosorbent assay (ELISA) tests with high specificity has been developed, using LPS-stripped elementary bodies as antigens. A recent study showed little difference in the major performance characteristics: the sensitivities of all MIFs and ELISAs were 100% for all assays (except ELISA by Vircell, with 90% sensitivity); specificity ranged from 92% for MIF Anti lab system to 98% for MIF Focus and ELISA Vircell. Evaluated ELISAs are comparable to MIFs in the detection of C. trachomatis IgG Abs and is preferred for large serological studies especially in resource poor setting.

**Summary**

C. trachomatis is the most common STD. Usually these unrecognized and untreated infections are known to increase the risk for tubal factor subfertility at a later age. Diagnostic Laparoscopy which is considered gold standard in diagnosing tubal pathology has been used in subfertility work up for a very long time and is known to be expensive and invasive. With advancement in lab technology,
Chlamydia antibody testing (CAT) has been introduced in the fertility work-up as an inexpensive and non-invasive screening test for tubal factor subfertility. Its diagnostic accuracy is affected by the antibody test used, the cut-off titre chosen for a positive test and cross-reactivity with C. pneumonia. This inexpensive and non-invasive screening test can reduce number of laparoscopies in resource poor settings like ours and burden on our healthcare professionals.

References


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