Can screening *Chlamydia trachomatis* by serological tests predict tubal damage in infertile patients?

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SUMMARY

Effectiveness of screening *Chlamydia trachomatis* (CT) antibody to predict tubal damage was assessed in this prospective study which was performed in a teaching hospital between September 2003 and September 2004. The study group consisted of 152 patients who underwent laparoscopy for infertility and the control group consisted of 80 fertile women who gave birth in the same hospital. CT antibody levels were measured by IFA (Indirect Fluorescence Assay for CT). Adhesions were defined by Gomel's classification system.

Rate of seropositivity of CT was 34.6% in the study group and 22.5% in the control group ($p>0.05$). In the study group, the sensitivity, specifity, positive predictive and negative predictive values of CT positivity for tubal damage were 40%, 69.5%, 50% and 60.2% respectively. In the infertile group, the rate of tubal adhesion in the CT positive group was 50% and in the CT negative group it was 39.7% ($p>0.05$). However, there was a positive correlation between the severity of tubo-peritoneal adhesions and seropositivity for CT.

In this study, we found out that tubo-peritoneal adhesions could not be predicted by the presence of CT inserum. There was a positive correlation between high CT seropositivity and high degree of adhesions.

KEY WORDS: Infertility, *Chlamydia trachomatis*, Tubal adhesion, Laparoscopy

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INTRODUCTION

Chlamydia trachomatis (CT) is a frequently diagnosed sexually transmitted disease. Generally it occurs as an asymptomatic infection and infertility and ectopic pregnancy risk is high due to its omnious sequelae (Macmillan *et al.,* 1999, Sharma *et al.,* 2002).

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It was estimated that 600.000 new cases with CT and 120.000 new infertility cases occur as a sequela of those who have had CT infection every year in Europe. Determining antibody levels in cervical mucus or in the serum is the easiest way to diagnose CT infection. In many clinics routine screening for CT was proposed to determine the reason for infertility. Cervical culture for CT is not a practical method to diagnose CT infection. Acute infection generally is asymptomatic and could not be diagnosed on a clinical basis. So it is important to diagnose the sequelae as a cause of infertility by the other methods such as hysterosalpingography (HSG) or laparoscopy. In our study, we aimed to assess the effectiveness of

screening CT with serological investigation as an indicator of tubal damage.

MATERIALS AND METHODS

This is a prospective study performed in Süleymaniye Maternity and Women's Disease Research and Teaching Hospital between September 2003 and September 2004. One hundred and fifty-two patients who applied to the infertility clinic and underwent laparoscopy were included in the study group. Eighty women who gave birth in our hospital served as a control group. In all, CT titers were measured in the serum samples of 232 cases in both groups. All CT titers were done in the hospital laboratory by IFA method (PANDIO Inc. MD USA). If the titer is greater than 1/10, test is considered positive. In the control group blood was drawn right after the delivery. *C. pneumoniae* IgA antibody was investigated in both the study and control groups by enzyme immune assay (EIA) (Vircell, SL, Spain).

Routine infertility testing including HSG (Hysterosalpingography), USG (ultrasonography), day 3 hormones (luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), estradiol (E2), prolactin (PRL) and sperm analysis for all husbands were performed. During laparoscopy methylene blue dye was injected through the cervical canal to confirm tubal patency. Gomel's classification (Audebert *et al.,* 1998) was used for adhesion scoring and *Chlamydia trachomatis* antibody titers and degree of adhesion were compared.

For statistical analysis Windows SPSS-11 programme was utilized. Parametric data were evaluated with Student's t test and non-parametric data with Q square test and correlation test. $p<0.05$ accepted as significant.

RESULTS

Patients with other causes of adhesion (history of pelvic surgery, endometriosis, tuberculosis) were excluded from the study. Only 3 cases were found to be positive for *C. pneumoniae* IgA in the study group but no positive case was positive in the control group. These 3 cases were among the already excluded 48 cases due to the above mentioned conditions. After exclusion, 36 antibody positive cases and 68 antibody negative cases remained in the study group. There was no statistically significant difference between groups with regard to age and duration of infertility ($p>0.05$). CT positivity was similar in the study (34.6%) and control groups (22.5%) ($p>0.05$) (Table 1). CT positive patients in the study group had titers between 1/10-1/ 360, whereas in the control group

TABLE 1 - *Chlamydia antibody titer.*

N	*Infertile group* *104*	*Controls* *80*	*p* *NS***
age	30.05 ± 5.6	27.32± 4.5	NS
CAT*(+)	36 (34.6%)	18 (22.5%)	NS
CAT (-)	68 (65.4%)	62 (77.5%)	NS

*CAT: Chlamydia antibody titer; **NS: non significant

TABLE 2 - *Chlamydia antibody titer in patients with tubal damage and controls.*

	Patients with tubal damage	*Controls*	*P*
CAT (+)	18 (40%)	18 (22.5%)	NS
CAT (-)	27 (60%)	62 (77%)	NS

TABLE 3 - *Degree of adhesion and Chlamydia antibody titer positivity.*

Degree of adhesion	*Chlamydia antibody titer (+)*	*Chlamydia antibody titer (-)*
No adhesion	18 (50%)	41 (60.30%)
Stage 0	1 (2.77%)	4 (5.88%)
Stage 1	3 (8.33%)	4 (5.88%)
Stage 2	1 (2.77%)	8 (11.7%)
Stage 3	11 (30.55%)	11 (16.1%)
Stage 4	2 (5.55%)	-
Total	36 (100%)	68 (100%)

There is a positive correlation between Chlamydia antibody titer and degree of adhesion ($p<0.05$) (r: 0.264).

titers of CT positive patients were between 1/10-1/180.

In the study group, 21 CT positive patients were primary infertile, 15 patients were secondary infertile and adhesion was encountered in 18 cases (50%). Fifty of the CT negative patients were primary infertile, 18 were secondary and 27 of them had various degrees of adhesions (39.7%). There was no statistically significant difference between CT positivity and adhesions in the study group ($p>0.05$).

Sensitivity for CT positivity for tubal damage was 40%, specificity was 69.49%, positive predictive value was 50%, and negative predictive value was 60.29%.

CT positivity was 40% in patients with adhesions in the study group (18+27) which was similar to the control group with no significant difference ($p>0.05$) (Table 2). However, there was a correlation between quantitative level of CT antibody titer and severity of adhesions (Table 3).

There was no relation between age and CT antibody presence ($p>0.05$).

DISCUSSION

In this study we tried to confirm whether CT antibody testing has a predictive value for detecting tubal damage. We found that CT antibody positivity in infertile women did not differ significantly from that of fertile women. But in infertile women who underwent laparoscopy, we found a linear correlation between high titers and severe tuboperitoneal adhesions.

In patients with CT antibody titer positive but no tubal damage, non-genital CT infection might be present giving rise to a cross reaction with *C. pneumonia* or *C. psittaci* or asymptomatic infection.

On the other hand, in patients with laparoscopically detected tubal disease but negative antibody titer, diminished antibody titer related to time has been considered as some authors agree but others do not (Puolakkainen *et al.*,1988, Henry-Suchet *et al.*,1994, Gijsen *et al.,* 2002). Immunity status in CT infections has not yet fully understood. Antibody presence in women with intact tubes shows that no attack of infection harms the tissue (Witkin *et al.,* 2002, Valentine 2003, Land *et al.,* 2003).

In one study, a negative correlation was detected between age and CT antibody titer in 1006 patients (Valentine *et al.,* 2003). However, we did not find any correlation between these parameters. This may due to monogamy and no sexual relationship before marriage in our country.

There are some reports on the high predictive value of CT antibody positivity on tubal damage (Valentine *et al.,* 2003, Tanikawa *et al.*, 1996). Combined use of medical history taking and CT testing has been reported to have a superior diagnostic accuracy than one of these alone. CTA testing adds additional predictive value to a woman's medical history risk profile (Coppus *et al.,* 2007). This means CT antibody testing has

not enough predictive value when used alone. In our study, CT antibody positivity in patients with tubal damage had 40% sensitivity and 69.49% spesificity. Positive predictive value was 50% and negative predictive value was 69.29% which was similar to above mentioned study.

The disease spectrum depends on the severity and extension of the adhesions. This is also confirmed by the linear correlation between quantitative CT antibody titer and adhesion score: the higher the titer the more the tubal damage was present (Valentine *et al.,* 2003, Tanikawa *et al*., 1996, Johnson *et al.*, 2000, Sheffield *et al.,* 1993). Our findings are compatible with this result. Same authors also recommend laparoscopy to patients with higher antibody titers. We also reached the same findings but since severe tubal damage was easily detected during routine infertility investigation, we do not recommend additional CT antibody testing to curb costs.

As a screening test CT serology has a wide range and is not more valuable than laparoscopy (Valentine *et al.,* 2003, Tanikawa *et al*., 1996, Johnson *et al.*, 2000, Sheffield *et al.,* 1993, Akande *et al.,* 2002) but can be used to determine pelvic damage risk before laparoscopy and to treat the infection at an earlier stage. We could not find a significant relation between CT antibody positivity and presence of tubal damage, namely the test has not a predictive value. For this reason, we do not recommend it as a screening test. It is also debatable to perform CT testing to treat the disease at an earlier stage. Empirical antimicrobial treatment may be more cost-effective than serology testing as it costs almost one sixth of serology. But antibiotic resistance should be kept in mind.

In a study which included 80 infertile patients, it was reported that HSG was not more predictive than CT serology in the diagnosis of peritubal adhesions, therefore CT antibody positivity was considered an indication for laparoscopy (Johnson *et al.,* 2000). In a recent study, two diagnostic methods, *Chlamydia trachomatis*–specific IgG and hysterosalpingography (HSG), were assessed as screening tests for the likelihood of tubal damage or occurrence of pregnancy before laparoscopy of subfertile women. *Chlamydia* antibody testing and HSG have comparable limited value in predicting pregnancy rates. No significant differences were found in cumulative pregnancy rate between CT IgG-negative and CT IgG-positive results. The diagnostic accuracy of *C. trachomatis*–specific IgG antibody testing is comparable with HSG, but both show poor performance. The prognostic value of occurrence of pregnancy of both tests is also poor. *Chlamydia* antibody testing as a screening test to estimate the risk of tubal pathology before laparoscopy is preferable to HSG owing to its simplicity and limited inconvenience (Perquin *et al.,* 2007). We detected tubal damage in 50% of CT antibody positive patients and there was tubal involvement in 39.7% of CT antibody negative individuals during laparoscopy. The difference was not significant. Therefore, this finding says us that CT antibody positivity is not an indication to perform laparoscopy.

Antibodies are well-correlated with infection episodes. But after the infection has passed antibodies either disappear or decrease to undetectable levels or remain a life-time. A positive CT antibody shows at least one episode of past infection, but a negative test does not eliminate CT infection (Veenemans *et al.,* 2002). This condition may help us to explain why CT antibody is negative although 39.7% of tubal damage is detected during laparoscopy. However, it is difficult to relate this tubal damage to *Chlamydia,* because diagnosis of definite etiology is almost impossible by routine laboratory investigation due to technical difficulties and cost. Since CT serology does not yield certain results we think it is useless to to perform it on a routine basis.

The aim of screening subfertile patients at risk of tubal damage is to determine past CT infection. However, various immune mechanisms, genetic factors, HLA tissue type, cytokine profile, infection load, access route of infection and endocrine status affect the immune response and serology results. Presence of IgG antibody is not always a sign of chronic infection but may be a sign of past and healed disease. All these limit the value of serology (Land *et al.,* 2003, Debattista *et al*., 2003) and support our decision to exclude CT serology from routine infertility testing.

In conclusion, CT antibody testing has no predictive value to consider tubal damage. For this reason it should not be used as a screening test. However, a linear correlation is encountered between quantitative level of antibody titers and degree of adhesion.

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