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Clinical algorithms for the screening of *Chlamydia trachomatis* in Turkish women

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Objective: To test the diagnostic validity of clinical algorithms for the detection of *Chlamydia trachomatis* in an urban population of married women in Turkey.
Design: Cross-sectional population-based survey.
Subjects: A systematic sample of 867 women who reported the use of contraceptive methods.
Main outcome measures: Sensitivity, specificity and positive predictive value of clinical algorithms for the diagnosis of *C trachomatis*.
Results: *C trachomatis* was diagnosed in 4·89% of the women. The WHO algorithm for use in settings where no vaginal examination could be performed had a sensitivity of 9% and a specificity of 96%. The corresponding figures for the WHO algorithm incorporating the findings of a speculum examination were 47% and 56% respectively. Algorithms incorporating symptoms or signs other than those suggested by the WHO did not yield satisfactory standards of validity.
Conclusions: The findings of this study do not support the widespread introduction of the use of clinical decision models for screening of women for chlamydia infection in primary health care settings such as family planning or antenatal clinics. The large number of false positive results with the use of the clinical algorithms tested in this study would cause unnecessary costs to the health system and unnecessary interventions to the women treated.
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Keywords: *Chlamydia trachomatis*; algorithm; screening

Introduction

Sexually transmitted diseases (STDs), particularly those due to *Chlamydia trachomatis* and *Neisseria gonorrhoeae* pose a major threat to the health of men and women throughout the world. In women, infections due to *C trachomatis* may cause severe acute complications such as pelvic inflammatory disease leading to serious sequelae including premature rupture of membranes, ectopic pregnancy and infertility.[1]

The diagnosis of STDs often requires the use of sophisticated and expensive laboratory equipment which may not be available in many settings, particularly in the developing world. For that reason, the World Health Organization (WHO) has developed simple diagnostic models in which symptoms reported by the woman and/or signs observed by the physician are used to arrive at a diagnosis.[2] Recently, the diagnostic algorithms have been revisited and an initial assessment of the woman's risk status based on her age, marital status and characteristics of her sexual partner(s) has been added to the algorithm.[3,4] Previous research has suggested that the inclusion of a risk assessment adapted to the local epidemiological context of STDs may increase the predictive power for the diagnosis of cervicitis due to *N gonorrhoeae* and *C trachomatis*.[5–8] Although the algorithms have been developed for the diagnosis of STDs in women who are seeking care for symptoms of vaginal discharge and/or lower abdominal pain, their use as a screening tool in women attending antenatal or family planning clinics has been proposed.[4,9,10] Little evidence, however, exists on the validity of such algorithms for active case finding in a population-based sample of women. For developing countries, the available evidence suggests that the diagnostic validity of clinical algorithms for the detection of *N gonorrhoeae* and *C trachomatis* may be poor.[5,8]

The objectives of this study were to test the diagnostic validity of clinical algorithms for the detection of *C trachomatis* in an urban population of married women in Turkey.

Methods

The study was carried out in Cobançesme, a rapidly growing suburb in the western part of Istanbul, the metropolis of Turkey. In 1986, all the households residing in the area were listed, and an update of the population has been maintained since by the Maternal and Child Health and Family Planning (MCH/FP) Centre. In 1993, the population of Cobançesme was approximately 25 000.

A systematic sample of 1204 currently married women between the ages of 15 and 44 years who reported they had ever tried to avoid a pregnancy was selected from the household register. Of these, 337 women were excluded because of out-migration (197), refusal (56), non-eligibility (33) and current pregnancy (51). The remaining women were visited at their home by two female interviewers, their socio-demographic characteristics and potential risk determinants for reproductive tract infections (RTIs) were noted and they were invited to attend the MCH/FP centre for further interview and examination by a physician.

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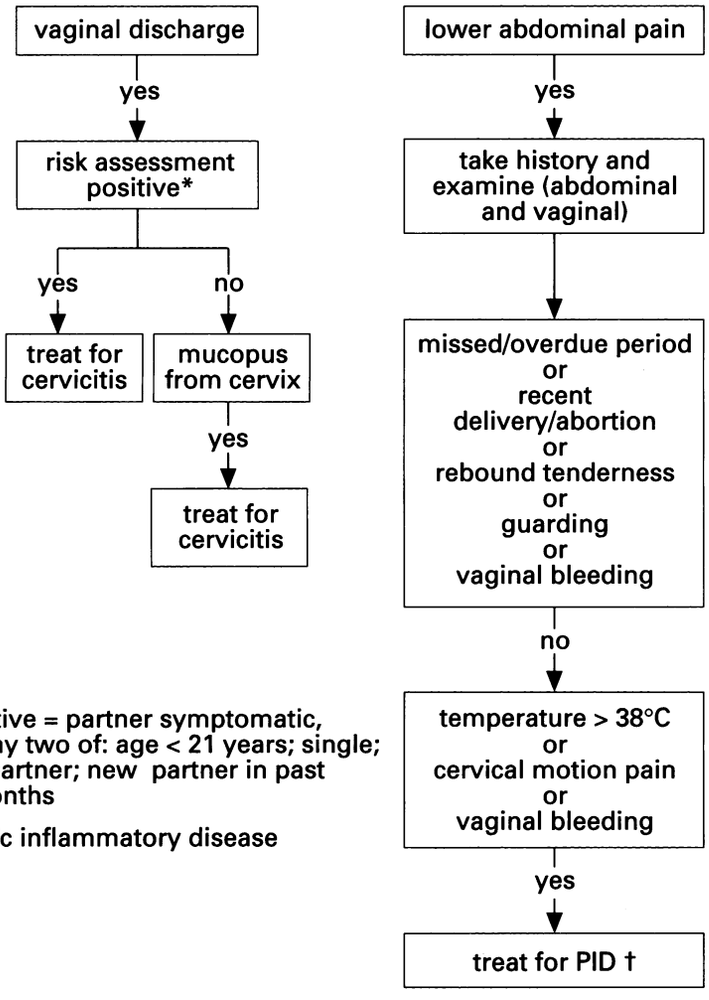
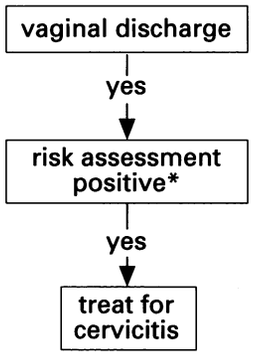
(a) Algorithm if vaginal examination possible



* positive = partner symptomatic, or any two of: age < 21 years; single; > 1 partner; new partner in past 3 months

† pelvic inflammatory disease

(b) Algorithm if vaginal examination not possible



* positive = partner symptomatic, or any two of: age < 21 years; single; > 1 partner; new partner in past 3 months

Clinical algorithm for the diagnosis of C trachomatis in women, based on the WHO-algorithm for vaginal discharge and lower abdominal pain.

Of the 867 women who were invited to attend the MCH/FP centre, 171 did not come to the clinic.

Between May 1993 and February 1994, 696 women were seen by three female primary care physicians in the MCH/FP centre. Two physicians (AB and NY) with extensive training and clinical experience in the diagnosis of RTIs carried out 43% of the examinations and one junior physician who had received one months' training in diagnosing RTIs carried out the remainder of the examinations. The physicians used a structured questionnaire to record the reproductive symptoms described by the women and performed a physical examination which included an abdominal, a speculum, and a bimanual examination. The amount, consistency and colour of the discharge within the vagina were recorded by simple inspection and, in case of uncertainty, by using a swab test[11]; the presence of cervical ectopy, easily induced endocervical bleeding and tenderness on moving the cervix were also noted.

A sample of the vaginal discharge was removed from the posterior fornix with a swab and tested for pH, and another sample was mixed with a drop of 10% KOH to assess the presence of a fishy odour. These samples were gram-stained and examined microscopically for the presence of clue cells, polymorphonuclear leucocytes, and fungal forms. Vaginal swabs from the vaginal side walls were cultured onto Trichomonas Liquid Medium (Oxoid-code: CM161) and examined microscopically for motile trichomonads. Women were considered infected with trichomonas if the vaginal culture was positive. A woman was diagnosed as having bacterial vaginosis if she presented three of the following findings: white and "mucoid or milky" and "moderate or abundant" vaginal discharge; vaginal ph > 4·5; positive KOH test; presence of clue cells in the gram stain.[12]

Cervical smears were examined microscopically for the presence of leucocytes and were fixed for PAP smear examination. Samples taken from the cleaned endocervix were assayed for *C trachomatis*, using an enzyme linked immunoassay (EIA) (IDEIA Chlamydia, DAKO Diagnostics Ltd, Cambridgeshire, UK). The positive results obtained by EIA were confirmed by direct fluorescent assay (DFA) (Micro Trak, Syva Co, Palo Alto, CA). One woman had to be excluded from the analysis because of invalid endocervical samples for *C trachomatis*.

Two clinical algorithms were assessed, one for use in settings where a vaginal examination is not possible and one for use in settings where a speculum examination is possible (fig).[3] The algorithms aim at identifying women with cervicitis or pelvic inflammatory disease (PID) due to *C trachomatis* and/or *N gonorrhoeae*. In first level settings where a vaginal examination can not be done, women are diagnosed with cervicitis if they complain of vaginal discharge and are at high risk of STDs. Women are considered at high risk of STDs when their partner is symptomatic or when they have any two of the following characteristics: they are younger than 21; they are single; they have more than one partner; or they have a new partner in the last 3 months. In settings where a clinical examination including a vaginal

Table 1 Selected characteristics of women with Chlamydia trachomatis in Instanbul, Turkey

Characteristic	Percent with characteristic: Women with C. trachomatis (n = 34)	Women without internal C. trachomatis (n = 661)	Odds Ratio 95% confidence
Risk determinants			
Age < 21 years	2·94	2·27	1·30 (0·17–10·18)
Husband discharge	11·76	5·34	2·37 (0·79–7·09)
IUD use	29·41	27·77	1·08 (0·51–2·31)
Condom use	8·82	9·71	0·90 (0·27–3·03)
Pill use	8·82	5·16	1·78 (0·52–6·11)
Vaginal "douching"	82·35	87·54	0·66 (0·27–1·65)
Reported symptoms			
Abnormal vaginal discharge	55·88	56·28	0·98 (0·49–1·97)
Vaginal itching	14·71	16·26	0·89 (0·34–2·35)
Malodorous discharge	23·53	25·15	0·91 (0·41–2·06)
Profuse discharge	23·53	11·04	2·48‡ (1·08–5·68)
Yellow-green discharge	11·76	12·88	0·90 (0·31–2·62)
Urinary complaints	29·41	38·18	0·67 (0·32–1·43)
Dyspareunia	35·29	37·35	0·91 (0·44–1·88)
Lower back pain	67·65	69·59	0·91 (0·44–1·91)
Lower abdominal pain	55·88	54·85	1·04 (0·52–2·09)
Clinical examination			
Abnormal vaginal discharge	52·94	50·23	1·11 (0·56–2·22)
Profuse discharge	2·94	4·12	0·71 (0·09–5·36)
Cheesy (clumped) discharge	8·82	4·57	2·02 (0·58–6·99)
Anine odour	18·18	16·07	1·16 (0·47–2·88)
Endocervical mucopus	11·76	14·33	0·80 (0·27–2·31)
Cervical ectopy	26·47	9·98	3·24§ (1·45–7·25)
Cervical friability	35·29	29·20	1·32 (0·64–2·73)
Pain on cervical motion	17·65	22·61	0·73 (0·30–1·80)
Laboratory results			
Microscopy			
Leucocytes (≥ 10/HPF*)	82·35	60·82	3·01§ (1·23–7·36)
PMN† (≥ 30/HPF)	47·06	23·60	2·88§ (1·43–5·78)
Clue cells	2·94	4·84	0·60 (0·08–4·49)

*HPF = high power field.
†PMN = poly morphonuclear leucocytes in Gram-stained smears from posterior fornix.
‡$p \leqslant 0{\cdot}05$; §$p \leqslant 0{\cdot}01$.

and an abdominal examination can be performed, women are diagnosed with cervicitis if they complain of vaginal discharge and are either at high risk of STDs or at low risk of STDs but the speculum exam reveals the presence of mucopurulent discharge from the cervix. In the latter setting, women who complain of lower abdominal pain are diagnosed with PID if they have a fever, pain on cervical motion, or vaginal discharge.

In this study, the standard against which the algorithms were assessed was a positive assay for *C trachomatis*. The performance of the algorithms were tested by simulating the decision trees using the distribution of the signs and symptoms observed in the sample and by calculating the sensitivity, specificity, and positive predictive value of a combination of signs and symptoms for the diagnosis of *C trachomatis*. Significant associations were tested using a chi square or a Fisher's exact test for comparing proportions.

In an attempt to improve the performance of the clinical algorithms, alternative algorithms were constructed based on the findings from the univariate analysis of the association between risk determinants, signs or symptoms and chlamydia infection. Variables that were found to be associated with chlamydia infection in the univariate analysis were incorporated in an algorithm, either alone or in combination, and their sensitivity, specificity, and positive predictive value for the diagnosis of *C trachomatis* was assessed.

Results

The 695 women who participated in the study had a mean age of 31·95 years (standard deviation: 6·21); a mean parity of 2·72 (SD:1·46); and 12·4% had received a secondary school education. In comparison, the 171 women who were not examined had a mean age of 29·12 years (SD:5·85); a mean parity of 2·27 (SD:1·33); and 24% had been to secondary school.

C trachomatis antigens were isolated in 34 (4·89%) of 695 women. The prevalence of *C albicans*, *Trichomonas vaginalis* and bacterial vaginosis was 5·18 (n = 36), 2·88% (n = 20) and 4·46% (n = 31) respectively. Among the women with chlamydial infections, 2 also had candidiasis, 2 also had trichomoniasis and 2 also had bacterial vaginosis.

The potential risk determinants, reported symptoms, signs on clinical examination and laboratory results for chlamydial infection are presented in table 1. Potential determinants for high risk of STDs such as young age or repeated vaginal douching were not associated with infection due to *C trachomatis*. Women with infection due to *C trachomatis* reported more often the presence of urethral discharge in their husband than those without, but this difference was not significant (odds ratio 2·37, 95% confidence interval 0·79–7·09). More than half of the women reported abnormal vaginal discharge or lower abdominal pain, but neither of these symptoms were associated with chlamydial infection, except for profuse discharge which was more commonly reported by women with chlamydial infection (odds ratio 2·48, 95% CI 1·08–5·68).

The physicians reported a higher prevalence of cervical ectopy in women infected with *C trachomatis*. Leucocytes and neutrophils were more commonly found in the discharge of women infected with *C trachomatis*.

The sensitivity, specificity and positive predictive value of the WHO algorithms are shown in table 2. In settings where a speculum

Table 2 Sensitivity, specificity and positive predictive value of algorithms for the screening of C trachomatis

Screening algorithm	Number of women*	Number of infected women	Number of cases detected	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)
WHO-algorithms						
Without vaginal examination	690	34	3	8·82	96·19	10·71
With vaginal examination	683	34	16	47·06	56·09	5·32
Alternative algorithms						
Reported discharge in husband	690	34	4	11·76	94·66	10·26
Reported discharge in husband and age < 25 years	690	34	0	0·00	99·54	0·00
Reported profuse discharge	686	34	8	23·53	88·96	10·00
Reported profuse discharge and cervical ectopy	686	34	1	2·94	98·47	7·36

*The number of women for which information on all the relevant variables was available.

examination can not be performed, the algorithm had a sensitivity of 8·82% and a specificity of 96·19% for the screening of women for chlamydial infection. Of the 28 women who satisfied the algorithm, 25 did not test positive for the EIA. Adding the findings of a speculum examination increased the sensitivity to 47·06% and decreased the specificity to 56·09%. With the latter algorithm, only 16 out of the 301 women who satisfied the algorithm would effectively have the disease (positive predictive value = 5·32%).

Multiple alternative algorithms were tested, of which only four are presented here (table 2). Women were regarded as infected with *C trachomatis* if (1) they reported urethral discharge in their husband; (2) they reported urethral discharge in their husband and were less than 25 years old; (3) they reported profuse vaginal discharge; and (4) they reported profuse vaginal discharge and cervical ectopy was found during vaginal examination. None of the algorithms yielded satisfactory standards of validity. The sensitivity was very low, ranging between 0 and 24%. This low sensitivity is due to the low prevalence of any of the tested characteristics amongst women with chlamydial infection. The positive predictive value was equally low, ranging from 0 to 10%.

Discussion

In this population, reproductive symptoms reported by the woman were very poor predictors of chlamydial infection. Although reports of vaginal discharge and abdominal pain were very common, they were not indicative of infection with *C trachomatis*, and this is consistent with the findings from other studies.[5-8 13]

Clinical signs such as mucopurulent discharge from the cervix,[6 14] induced endocervical bleeding[6 7 14] and cervical ectopy[7] are usually more predictive of chlamydial infection than reported symptoms, although their low prevalence makes them not very useful for screening purposes.[5] Cervical ectopy was strongly associated with chlamydial infection in this study, but was only present in 26% of the chlamydial infections, hence cervical ectopy on clinical examination would be too insensitive for use in the screening of women for chlamydial infection.

Mucopurulent discharge from the cervix, the key sign by which clinical algorithms usually distinguish women with chlamydial infection from those without,[2 4 11] was not found to be a good predictor of chlamydial infection in this study. The physicians carrying out the clinical examination were experienced in examining women for signs of STDs, but only performed the recommended swab test if they were uncertain about the presence of mucopurulent discharge on inspection of the cervix. Objective signs of cervical inflammation may be difficult to diagnose because of changes in the cervix over the reproductive period and with the menstrual cycle.[15] Mucopurulent discharge was associated with trichomoniasis (data not shown), which suggests that the yellow-green discharge commonly associated with trichomonas[16] may be difficult to distinguish from "mucopurulent" discharge.

Incorporation of one or more risk determinants into the algorithm such as young age,[5 8 14] being unmarried,[5 8] having had more than one sexual partner in a relatively recent period[5-8 13] or having changed partners recently[7 13 14] usually increases the sensitivity and specificity of the algorithm. In this population, risk assessment questions did not help distinguish chlamydial infections from other infections. All the women were married and the majority of the women examined were older than 25 years, and age was thus not a predictor of chlamydial infection. A report of discharge in the husband was too uncommon to be of value for screening purposes, and it was not deemed acceptable to ask questions about the number of sexual partners. If risk-criteria based on the local epidemiological profile and on behavioural rather than clinical characteristics are to be recommended for inclusion in algorithms for the diagnosis of RTI, care will have to be taken to assess the reliability and validity of the risk-criteria in the specific context in which they are to be applied.

This study did not test for the presence of *N gonorrhoeae*, one of the major causes of cervicitis in women. Since the WHO algorithms aim at identifying women with cervicitis rather than women with chlamydial infection, the women with gonococcal cervicitis may have been incorrectly classified in this study, and the validity of the algorithms may have been mis-specified. Other studies testing for the presence of *N gonorrhoeae* amongst Turkish women, however, have found no or very low prevalences of gonococcal infections amongst women[17-19] and it is unlikely that this misclassification would have caused a major bias in the estimates of sensitivity and specificity in this study. Other studies assessing the validity of clinical algorithms for the diagnosis of both chlamydial and gonococcal infections have also yielded very poor results in low prevalence populations.[5 8]

The enzyme immunoassay used as a standard for the diagnosis of chlamydial infection in this study has a specificity approaching 100% for the detection of *C trachomatis*, but the sensitivity may be poor.[20] A fraction of the women with chlamydial infection may have been wrongly classified as not having the disease, biasing the estimates of the specificity of the clinical algorithms. The magnitude of this bias, however, is small, given the low prevalence of chlamydial infection in this population.

The fact that one fifth of the women refused to participate in the study is a matter for concern, particularly since efforts were made to prevent such a problem. This high non-response rate poses a threat not only to the validity of the results but also to the effective control of STDs. The women who did not participate were younger and more educated than those who did, and did not want to be examined because they perceived they had no problems. Although impossible to ascertain, their younger age may have put them at higher

risk for STDs, particularly to infections due to *C trachomatis*.[5] That women may perceive STD services as stigmatising is well known,[21] but it is particularly worrying that the young and possibly most vulnerable group are the ones refusing to be examined.

The findings of this study do not support the widespread introduction of the use of clinical decision models for screening of women for *C trachomatis* in primary health care settings such as family planning or antenatal clinics. The large number of false positive test results with the use of any of the clinical algorithms tested in this study would cause unnecessary costs to the health system and to the women treated. Finding rapid, simple and cheap tests for the diagnosis of *C trachomatis*, such as the recently developed urine assay[22] remains a major priority for reproductive health research.

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