Accuracy of tests used to detect infection with Chlamydia trachomatis in asymptomatic pregnant women: a systematic review

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Abstract

Purpose of review

Infection with Chlamydia trachomatis in pregnancy is linked to increased risk of miscarriage, stillbirth, and preterm birth. Currently, PCR or DNA-based tests are the gold standard when detecting the infection; however, they are costly and require access to specialist equipment. The aim of this systematic review was to assess the accuracy of available tests to detect infection in an asymptomatic pregnant population.

Recent findings

There was evidence of the superior accuracy of nucleic acid amplification tests to cell culture in non-pregnant asymptomatic women; however, there are multiple commercial nucleic acid amplification tests with varying sensitivities and specificities. There is a gap in current literature on accuracy studies in an asymptomatic pregnant population, particularly within routine antenatal settings.

Summary

There is a need for a point-of-care test for Chlamydia in pregnancy. Future test accuracy studies for this population should aim to use a universally established reference standard. Further research should provide relevant evidence to guide practice.

Keywords

antenatal care, Chlamydia trachomatis, point-of-care test, sexually transmitted infections
Introduction

Chlamydia trachomatis, commonly referred to as chlamydia, is the most common sexually transmitted infection (STI) worldwide with 105.7 million cases [1]. Of this, the largest proportion is within south and southeast Asia, and sub-Saharan Africa [2]. Early detection is a key in order to prevent complications, such as cervicitis, urethritis, and pelvic inflammatory disease; however, 70–80% of infected women are asymptomatic [3]. The infection is most commonly transmitted through sexual intercourse and can also be passed from mother to baby in utero or during birth. Untreated infections of pregnant women have been linked to newborn blindness [2], miscarriage, stillbirth, and preterm birth. The treatment of chlamydial infections with antibiotics such as erythromycin has been shown to be efficacious in preventing these adverse outcomes, as well as the transmission to the newborn. Therefore, the identification of a suitable screening test is important in order to isolate C. trachomatis within an asymptomatic pregnant population and provide treatment [4].

The major obstacle in controlling and preventing of Chlamydia infection within resource-limited settings is the unavailability of reliable, low-cost, point of care tests (POCTs) which detect and treat the infection during the same visit [5]. Current reviews assessing the accuracy of tests detecting C. trachomatis identify PCR or DNA-based tests as the best performing tests; however, their study populations were not specific to a pregnant population[6,7]. The aim of our work was to review and synthesize the accuracy of tests used in an asymptomatic pregnant population to detect infections with C. trachomatis

KEY POINTS

- There is evidence for application of NAAT-based testing in an asymptomatic pregnant population.
- There are multiple commercial NAATs available with varying sensitivities and specificities.
- Future test accuracy studies for this population should aim to use a universally established reference standard.

MATERIALS AND METHODS
The search strategy was run in EMBASE, MEDLINE (OVID), SCOPUS, and Web of Science with no language restrictions. A supplementary search was also conducted in LILACS and GreyOpen, a database with grey literature. The search was run from inception up to February 2015, updated in February 2016 and June 2017. No time limit was included in the search filter.

Study selection

Two independent reviewers (S.V.S. and S.S.) screened references and then the full texts of potentially relevant articles of the initial search (up to February 2015). The reference screening for the two updates was done only by one reviewer (S.V.S.). The study had to meet the following eligibility criteria: recruit pregnant women without symptoms of Chlamydia, carrying a single fetus with no history of preterm delivery. We included studies where the data were presented as true positive, true negative, false negative, false positive, or as sensitivity, specificity, positive predictive value, negative predictive value, and sample size. We excluded studies in which the pregnant population showed symptoms of Chlamydia. At each stage of the review process, the consensus was reached through a discussion. In the case of disagreement, the opinion of a third reviewer was sought (E.R.).

Data extraction and study quality assessment

Following data were extracted from the studies: characteristics of the study, e.g., study design, recruitment setting, inclusion/exclusion criteria, as well as information on the index and reference tests being compared. The information on the tests included specimen collection, storage, testing, and interpretation of the tests. The quality assessment was conducted by two reviewers (E.R. and S.V.S.) using the QUADAS-2 tool [8]. The study quality was assessed in four domains: patient selection, choice of the index test, choice of the reference standard, and the flow of patients through the study. The studies were classified as ‘low’, ‘high’, or ‘unclear’ for the level of risk of bias. The details of QUADAS-2 are included in the data extraction form (see SDC). Numeric data were imputed into the Review Manager (RevMan) software (version 5.1, Copenhagen; The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS
Characteristics of included studies

We identified 12 studies evaluating accuracy of onsite tests to detect infections with C. trachomatis among pregnant women. The studies were published between 1986 and 2006 with no new studies identified within the last year. The studies evaluated the following tests: PCR, direct enzyme immunoassay (MicroTrak SYVA), direct immunofluorescence assay (MicroTrak SYVA), Chlamydiazyme (Abbott Laboratories), chlamydia immunoglobulin A (IgA) Rapid SeroTest ELISA (Savyon Diagnostics), Gen-Probe PACE 2 (Gen Probe Inc AQ8. ), immunoglobulin G (IgG) level via immunofluorescence techniques, Papanicolaou smear, and wet mount gram stain (Table 1) [9–20]. Seven studies recruited women in antenatal care settings [9–15] and five women who were present at the clinic for termination of pregnancy [16,17–20]. The prevalence of the infection ranged from 2 to 87%. All studies except one [11] were carried out in high-income countries (Table 2) [9–20].

Quality assessment

A total of 8 out of 12 included studies did not provide sufficient description of women’s enrolment (unclear risk of bias). The majority of the studies were assessed as a low risk of bias regarding implementation of the index test (Table 3) [9–20]. The risk of bias in 75% (9/12) of studies on the reference standard was considered as unclear due to insufficient information. The risk of bias for flow and timing was unclear in two studies [14,18] and high in one [19]. Women in five studies were recruited from termination clinics. Therefore, the concern regarding the applicability of population from those studies was considered as high. The applicability of index tests in most studies was good (low concern). The use of the cell culture as a reference standard due to change of diagnostic standards resulted in eight studies being labelled as an unclear concern of applicability for the reference standard.

Cell culture as reference standard

Nucleic acid amplification tests

One study reported the sensitivity of the Gen-Probe PACE 2 assay to be 93.9% [confidence interval (CI) 95% 79.8–99.3] and specificity 99.1% (CI 95% 96.7–99.9). Another study assessed the accuracy of PCR (Ampl-Taq Polymerase) method in comparison to cell culture. The sensitivity of PCR was 77.8% (CI
95% 40.0–97.2) and specificity 99.2% (CI 95% 97.7–99.8) [20]. Another study used a PCR method with plasmid primers had sensitivity 90.0% (CI 95% 78.2–96.7) and specificity 92.6% (CI 95% 82.1–97.9) when compared with the Pathfinder [18].

Enzyme-linked immunoassays

Accuracy data for SYVA MicroTrak (Syva Company) [20] and Chlamydiazyme (Abbott Laboratories) [15] were reported in two separate studies. Chlamydiazyme had a higher sensitivity at 90.9% (CI 95% 58.7–99.8) compared with SYVA Microtrak at 75% (CI 95% 42.8–94.5), but had a lower specificity at 97.9% (CI 95% 92.6–99.7) compared with Microtrak’s 98.3% (CI 95% 96.5–99.3).

Papanicolaou smear

Two studies reported the accuracy of Papanicolaou smear test in comparison to cell culture. One study reported sensitivity and specificity to be 11.1% (CI 95% 28–48.25) and 98.1% (CI 95% 93.2–99.8), respectively; [11] whereas the other study reported it as 60.5% (CI 95% 44.4–75.0) and 56.4% (CI 95% 50.1–62.6) [19].

Direct immunofluorescence assay

One study reported SYVA MicroTrak’s direct immunofluorescence assay (DFA) technique [20] sensitivity and specificity as 81.3% (CI 95% 48.2–97.7) and 99.5% (CI 95% 98.2–99.9) respectively.

Microimmunofluorescence

Three different titres of cervical antibodies were visualized using microimmunofluorescence techniques in the same study [12]: IgA 8 or less, IgG 8 or less, and IgG 16 or less. The sensitivity of the titres was 59.1% (CI 95% 36.4–79.3), 63.4% (CI 95% 40.7–82.8), 45.5% (CI 95% 24.4–67.8), respectively, accompanied by specificity of 95.3% (CI 95% 93.8–96.5), 93.9% (CI 95% 92.3–95.3), and 98.4% (CI 95% 97.4–99.1) respectively.

Immunoperoxidase assay
One study detected serum IgG and IgA antibodies using a single serovar (L2) immunoperoxidase assay [17]. The two titres used were IgG 16 or less and IgA 8 or less. The sensitivity of IgG 16 or less as a titre was 95.2% (CI 95% 76.2–99.9) and specificity 43.4% (CI 95% 33.8–53.4). The sensitivity and specificity of IgA 8 or less titre were reported as 52.4% (CI 95% 29.8–74.3) and 81.3% (CI 95% 72.4–88.1) respectively.

Gen-probe PACE 2 as reference standard

Wet mount gram stain

Two studies reported data comparing Wet mount gram stain to Gen-Probe PACE 2 with varying results in sensitivities and specificities. One study reported a sensitivity of 91.4% (CI 95% 76.9–98.2), [9] whereas the other reported 86.7% (CI 95% 69.3–96.2) [10]. The specificities were calculated to be 18.0% (CI 95% 14.7–21.7) and 33.6% (CI 95% 28.3–39.1), respectively.

PCR

One study reported PCR technique to have a 100% (CI 95% 90.0–100) sensitivity and 98.3% (CI 95% 96.8–99.3) specificity when compared with Gen-Probe PACE 2 [9].

Other reference standards

Enzyme-linked immunoassays vs. ligase chain reaction

One study compared Clearview Chlamydia MF test which utilizes enzyme-linked immunoassays (EIA) techniques to detect Chlamydia, to ligase chain reaction but it used PCR as an arbiter. Sensitivity was low at 66.7% (CI 95% 44.7–84.4); however, specificity was 100% (CI 95% 99.0–100) [16].

Enzyme-linked immunoassays and direct immunofluorescence assay vs. PCR

One study compared Chlamydia IgA Rapid SeroTest, which utilized an EIA technique, to Amplicor PCR and reported a sensitivity of 95.6% (CI 95% 78.1–99.9) and specificity of 93.1%(CI95%87.7–96.6).The same study compared Chlamydiazyme, a DFA technique, to the same reference standard of Amplicor.
PCR and reported a sensitivity of 69.6% (CI 95% 47.1–86.8) and specificity of 97.2% (CI 95% 93.0–99.2) [15].

DISCUSSION

Gen-Probe PACE 2 had the highest sensitivity compared with cell culture out of all evaluated tests compared. PCR had the highest sensitivity compared with the Gen-Probe PACE 2.

Strengths and limitations

The search strategy was also designed in a systematic way using established, published filters to capture test accuracy studies [21]. The majority of the included studies had an unclear risk of bias concerning patient selection, where the risk of bias was labelled as unclear with respect to the index test and reference standard, it was mainly due to a lack of information about blinding of technicians.

There were significant concerns over the applicability of the sample population as some studies recruited pregnant women who were presenting for termination of pregnancy, a higher risk population, potentially giving the tests an inflated accuracy compared with women presenting for routine antenatal care who are a lower risk population. The prevalence rates within the antenatal setting ranged from 2.04% to 13.8% and from 2.36% to 48.1% within termination clinics. If a higher sensitivity and specificity is assumed to indicate a higher accuracy, recruitment setting does not appear to affect accuracy in a consistent manner.

The test accuracy of the Papanicolaou test was higher when participants were recruited from the antenatal clinic, whereas the inverse was true for the DFA (Microtrak) test where test accuracy was higher in the abortion clinic setting.

There were further concerns over a suitable reference standard for detecting Chlamydia. The ideal study of test performance would involve comparison with a recognized gold standard. However, in the field of Chlamydia research, there is little agreement on a recognized gold standard although it is commonly acknowledged that the traditional gold standard of culture does not perform as well as the newer tests [6]. Today, few laboratories in the United Kingdom offer culture as a service as they are expensive, labor
intensive, and time-consuming. The sensitivity is no more than 75% and is no longer used for medicolegal purposes [22]. In nonpregnant populations, NAAT testing has been proven in multiple studies to provide superior sensitivity and specificity [23–25] and is now the recommended method of diagnosis. One included a study that compared the Gen-Probe PACE 2, a recognized assay for Chlamydia testing, to culture revealed a high sensitivity and specificity. Another study that compared PCR to Gen-Probe PACE 2 found excellent results for PCR with 100.0% sensitivity and 98.3% specificity. However, they did not use a commercially available kit, thus diminishing clinical applicability.

There are a number of commercial NAATs currently available for routine use, those commonly used in clinical practice include: Abbott RealTime PCR assay (Abbott Diagnostics), BD ProbeTec ET (SDA, Beckton Dickinson), COBAS Taqman PCR assay (Roche Diagnostics), and GenProbe Aptima assay (TMA, GenProbe) [22]. However, none of these were used as either an index or a reference test in the included studies for this review. Considering also that the most recent included study was published in 2006, it highlights that research into test accuracy within the asymptomatic pregnant population is out-of-date and requires updating using NAATs as a reference standard. Recently, an ‘expanded gold-standard’ has been identified as Chlamydia diagnosed by two nonculture tests [6,26]. A single, commonly acknowledged reference standard in test accuracy studies for Chlamydia will enable useful comparisons to be drawn.

Interpretation

Currently, one review has addressed the issue of test accuracy in an asymptomatic, young female population using meta-analysis and metaregression [6]. It concluded that NAATs used on non-invasive samples such as urine were more effective at detecting asymptomatic infection, but acknowledged that limited data existed to correlate a positive result with clinical outcome. Another review has qualitatively analysed existing POCTs and concluded that Xpert CT/NG, a form of NAAT was the best performing test [7,27]. The evidence supporting the use of NAATs in a non-pregnant population is compelling, and there is large potential for its applicability to the asymptomatic pregnant population.
The diagnosis of Chlamydia in pregnancy is important, as infection during pregnancy has been shown to have four-fold increased risk of preterm labour before 32 weeks’ gestation [28,29]. The availability of a simple and affordable treatment for Chlamydia through the administration of antibiotics also makes the possibility of reducing preterm labour through treatment of Chlamydia extremely realistic. As such, the analysis of the accuracy of available tests would have been instrumental.

CONCLUSION

This systematic review has identified a gap in current literature for test accuracy studies in an asymptomatic pregnant population, particularly in antenatal settings. The evidence underlying the risks of chlamydial infection in pregnancy is compelling. Future test accuracy studies for this population studies should aim to use a new, universally established reference standard with a specific NAAT or combination of NAATs to be considered as options. However, further research should provide more evidence to strengthen this claim.

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Conflicts of interest

There are no conflicts of interest.
REFERENCES


22. Chlamydia trachomatis UK Testing Guidelines Clinical Effectiveness Group British Association for Sexual Health and HIV.


## Table 1: Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study Authors and Year</th>
<th>Location</th>
<th>Test used</th>
<th>Sample type</th>
<th>Reference test</th>
<th>Country</th>
<th>Setting</th>
<th>Income level</th>
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<td>Wet Mount Gram stain</td>
<td>Endocervical swab</td>
<td>Gen-Probe Pace 2 (Gen Probe Inc, San Francisco, Calif)</td>
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<td>Chlamydiazyme (Abbott Laboratories)</td>
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### Table 2: Study Quality Assessment using QUADAS-2 tool

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