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Chlamydia trachomatis-Specific Antibody Responses in Women in Cameroon with Secondary Infertility

Madison D'Amico, BS[*], **J Clarisse Engowei Mbah, MSc**[†,‡], **Kanupriya Gupta, PhD**[*], **Jodie A. Dionne, MD, MSPH**[*], **Jane Francis Akoachere, PhD**[†], **Jules Clement Assob Nguedia, PhD**[§], **Barbara Van Der Pol, PhD, MPH**[*], **William M. Geisler, MD, MPH**[*]

[*]Department of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham, AL, USA

[†]Department of Microbiology and Parasitology, University of Buea, Buea, Cameroon

[‡]Institute of Medical Research and Medicinal Plants Studies, Center for Research on Health and Priority Pathologies, Yaoundé, Cameroon

[§]Department of Laboratory Medicines, Faculty of Medicine and Pharmaceutical Sciences, University of Douala, Douala, Cameroon

Abstract

The contribution of chlamydia to secondary infertility in women is poorly understood. Among 404 female participants enrolled in a previous study in Cameroon, 142 with secondary infertility (cases) and 262 pregnant with no history of infertility (controls), *Chlamydia trachomatis* seropositivity was 92%. Seropositivity did not significantly differ by case/control status.

Short Summary

In a cohort of women in Cameroon with secondary infertility (cases) or current pregnancy (controls), *Chlamydia trachomatis* seropositivity was 92% and did not significantly differ by case/control status.

Keywords

chlamydia; antibody; seroprevalence; secondary infertility

INTRODUCTION

Chlamydia trachomatis (CT) infection remains highly prevalent worldwide, especially in Africa,[1,2] and it has a major impact on reproductive health in women. CT cervical infection can ascend into the upper female genital tract and cause pelvic inflammatory disease (PID), which can lead to sequelae including tubal infertility.[3,4] Female infertility is separated into

Corresponding author: William M. Geisler, UAB STD Program, 703 19th St. South, 242 Zeigler Research Building, Birmingham, AL, USA 35294-0007. Phone: 1 (205) 934-4376, wgeisler@uabmc.edu.
Madison D'Amico and J Clarisse Engowei Mbah are co-first authors

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primary or secondary based upon history of clinical pregnancy. Primary female infertility is defined as infertility (failure to achieve a clinical pregnancy after ≥1 year of unprotected sexual intercourse) in a woman who has never had a clinical pregnancy, while secondary female infertility is infertility in a woman who has had at least one clinical pregnancy.[5] The contribution of CT to secondary female infertility is not well understood.

Infertility is a major health concern among women in sub-Saharan Africa, where total fertility rate (births per woman) has been declining (6.3 in 1990 and 4.6 in 2019); this decline may be in part due to increased uptake of contraception, but could also be impacted by other factors, such as STIs.[6] In Cameroon, the infertility rate among women is as high as 30%, with secondary infertility more common than primary, compared to 11% among women in the US.[7,8] Studies have documented stigmatization and violence targeting women with infertility in Africa.[7, 9, 10] We previously investigated STI prevalence in women in Cameroon with secondary infertility or current pregnancy and found the overall prevalence of active CT infection (detected by nucleic acid amplification testing [NAAT]) was 4%; active CT infection was not associated with secondary infertility.[10] Since it is likely that CT-associated tubal damage reflects prior CT infections rather than active infection, studies incorporating CT antibody evaluations could advance our understanding of secondary infertility. The objective of our current study was to determine if the presence and/or magnitude of CT-specific antibodies was associated with secondary infertility among women in Cameroon.

MATERIALS AND METHODS

The current study was a retrospective case control study of CT seropositivity among women previously enrolled in a study in Southwest Cameroon that evaluated associations of current STIs with secondary infertility.[10] Enrolled women either had a diagnosis of secondary infertility ("cases" – unable to conceive after at least one year of unprotected sexual intercourse after a previous delivery) or were considered fertile ("controls" – pregnant women without a reported history of infertility). The parent study collected sociodemographic and clinical data by interview and medical record review and conducted NAAT (Hologic® Aptima®) on endocervical swab specimens for four STIs: CT, *Neisseria gonorrhoeae*, *Mycoplasma genitalium*, and *Trichomonas vaginalis*. Among 416 enrolled women, samples and clinical data were available from 404 women (142 cases and 262 controls). The study was approved by the Faculty of Health Sciences Institutional Review Board in Cameroon.

CT antibodies were measured in stored serum specimens at the University of Alabama at Birmingham (Birmingham, AL, USA) using a CT elementary body (EB) ELISA by previously described methods.[11,12] This EB ELISA uses alkaline phosphatase–labeled mouse antihuman IgG1 and IgG3 to detect anti-CT IgG1 and IgG3 responses, respectively. Serum samples, diluted 1:32, are run in triplicate and are considered positive for anti-CT IgG1 and IgG3 if their OD_{405} values are ≥0.35 and ≥0.1, respectively.

Analyses were conducted on Stata (version 14.0, StataCorp, College Station, TX). Associations of participant characteristics with case control status and with CT

seropositivity and magnitude of CT antibody responses were evaluated for using Fisher's exact, Chi-squared, and Wilcoxon rank sum tests as appropriate, with $P < 0.05$ as the cutoff for statistical significance.

RESULTS

Participant characteristics of the 404 women are shown in Table 1. Median age was 29 years, 85.4% reported 1–5 lifetime sexual partners, and 1.5% reported having more than one sexual partner at the time of the survey. Prior pregnancy complications included miscarriage in 20.1%, stillbirth in 3.5%, and ectopic pregnancy in 2.0%. One or more active STIs was detected in 15.5%: CT 4.5%, *N. gonorrhoeae* 2.4%, *M. genitalium* 6.8%, and *T. vaginalis* 3.4%.

There were significant differences in participant characteristics in cases vs. controls (Table 1): cases were older (median age 32 vs 27, $P < 0.0001$) and more often reported a white collar occupation (34.5% vs 20.6%, $P = 0.001$), >5 lifetime partners (26.4% vs 6.9%, $P < 0.001$), history of miscarriage (29.6% vs 14.9%, $P < 0.001$), and history of ectopic pregnancy (4.2% vs 0.8%, $P = 0.025$). Regarding current STI NAAT data, cases less often tested positive for any current STI (10.6% vs. 18.3%, $P = 0.045$) and specifically had a significantly lower TV NAAT positivity frequency (0.7% vs. 5.0%, $P = 0.037$).

Overall CT seropositivity (seropositive for either anti-CT IgG1 or IgG3) was detected in 372 (92.1%) of women: 364 (90.1%) were IgG1 seropositive and 278 (68.8%) were IgG3 seropositive. Differences in participant characteristics based on CT seropositivity status are shown in Table 2. CT seropositivity was associated with a younger age of sexual debut (79.6% of CT seropositive participants were age <20 years at sexual debut vs. 61.3% of CT seronegative; $P = 0.03$), while CT seronegative participants more often reported a history of miscarriage (37.5% vs 18.6%, $P = 0.01$). There was no significant difference between cases vs. controls with respect to CT seropositivity (92.3% vs 92.0%, $P = 0.92$), IgG1 seropositivity (91.6% vs 89.3%, $P = 0.47$), IgG3 seropositivity (64.1% vs 71.4%, $P = 0.13$), or magnitude of the IgG1 (median OD_{405} 1.319 vs 1.176, $P = 0.34$) or IgG3 (median OD_{405} 0.350 vs. 0.351, $P = 0.69$) responses.

The relationship of CT seropositivity and case control status was also analyzed in a subset of 45 women whose infertility status was based on hysterosalpingogram (HSG) findings rather than a clinical definition of infertility, with 36 having infertility findings on HSG (cases – tubal occlusion, salpingitis, or hydrosalpinx; uterine adhesions) and 9 having a normal HSG (controls – normal findings including patent tubes). There was no significant difference among cases vs. controls with respect to CT seropositivity (86.1% vs. 88.9% vs $P = 1.0$), IgG1 seropositivity (86.1% vs. 88.9%, $P = 1.0$), IgG3 seropositivity (55.6% vs 55.6%, $P = 1.0$), or magnitude of the IgG1 response (OD_{405} 1.137 vs. 1.129, $P = 0.73$) or IgG3 response (OD_{405} 0.346 vs. 0.558, $P = 0.41$).

DISCUSSION

To evaluate the association between historical CT infection and secondary infertility, we used CT EB ELISA to assess for prior CT infection based on CT seropositivity and did

not find an association with secondary infertility. CT seropositivity frequency was nearly universal in both groups (92% for both). The high CT seroprevalence in cases and controls reflects high lifetime CT exposure in this population of sexually active women in Cameroon. When the seropositivity is paired with the low number of CT NAAT positive women in both groups, data strongly suggest that many of these women had CT infections when they were younger. This is supported by global CT epidemiology with CT positivity rates consistently highest among women ages 15–29.[13] In our study, 76% of the participants were ≥25 years of age but 78% had their sexual debut <20 years of age. In the Cameroon general population, CT screening in asymptomatic women is not routinely recommended; when CT testing is performed in symptomatic women, it is usually not CT NAAT due to lack of availability. Therefore, it is likely that many CT infections are missed in Cameroon women at younger ages, putting some of these adolescents and young adult women at risk for future tubal infertility.

Another explanation for our finding of lack of association of chlamydia seropositivity with secondary infertility is that the CT EB ELISA is unable to distinguish CT seropositivity due to prior uncomplicated lower genital tract infection versus complicated upper genital tract infection. This is further supported by an earlier study in which we found no difference in CT seropositivity frequency based on CT EB ELISA in Black women enrolled at clinics in two U.S. cities (Birmingham and Pittsburgh) with tubal factor infertility (TFI) vs. other infertility etiologies (81% vs. 78%);[14] in this same cohort of Black women, another CT antibody assay, a CT Pgp3 ELISA, was also not associated with TFI.[15] Thus, CT serological assays that are more specific for CT-associated upper genital tract pathology will be needed for future studies aimed at better understanding the contribution of chlamydia towards reproductive complications in populations of women with high frequency of CT infections.

Our study was also limited in that data on prior CT infection episodes was not available for most participants (given CT testing is infrequent in this population) and this may have been helpful in better understanding impact of timing and number or prior CT infections on secondary infertility risk. Another limitation was that we could only assess secondary infertility in most women based on a clinical definition since infertility evaluation by more objective measures, such as HSG, was not conducted in most women. Finally, it is possible our findings may not be generalizable to populations with different sociodemographic characteristics.

In conclusion, our study found that in a cohort of women in Cameroon who had secondary infertility or were pregnant without a history of infertility, over 90% were CT seropositive, and seropositivity did not differ between the two groups of women.

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Table 1.

Participant Characteristics by Case (Secondary Infertility) vs. Control (Pregnant) Status

Variables	Total (n=404)	Case (n = 142)	Control (n = 262)	*P* *
Sociodemographics				
Median age, years (range)	29 (15–46)	32 (21–42)	27 (15–46)	<0.0001
Age, years				
15–24	95 (23.5%)	14 (9.9%)	81 (30.9%)	<0.001
25–29	126 (31.2%)	39 (27.5%)	87 (33.2%)	
30–39	121 (30.0%)	51 (35.9%)	70 (26.7%)	
40–46	62 (15.4%)	38 (26.8%)	24 (9.2%)	
Occupation†				
White Collar	103 (25.5%)	49 (34.5%)	54 (20.6%)	0.001
Business	182 (45.1%)	67 (47.2%)	115 (43.9%)	
None	74 (18.3%)	15 (10.6%)	59 (22.5%)	
Student	45(11.1%)	11 (7.8%)	34 (13.0%)	
Marital Status				
Single, Divorced or Widowed	137 (33.9%)	47 (33.1%)	90 (34.4%)	0.800
Married	267 (66.1%)	95 (66.9%)	172 (65.7%)	
Education				
None or Primary	73 (18.1%)	24 (16.9%)	49 (18.7%)	0.635
Secondary, High School or Vocational	231 (57.2%)	79 (55.6%)	152 (58.0%)	
University	100 (24.8%)	39 (27.5%)	61 (23.3%)	
Sexual History				
Age of sexual debut, years				
<14	14 (3.8%)	6 (4.3%)	8 (3.5%)	0.832
14–19	273 (74.2%)	106 (75.2%)	167 (73.6%)	
≥20	81 (22.0%)	29 (20.6%)	52 (22.9%)	
Lifetime sex partners				
1–5	304 (85.4%)	103 (73.6%)	201 (93.1%)	<0.001
≥5	52 (14.6%)	37 (26.4%)	15 (6.9%)	
Currently more than one sexual partner	6 (1.5%)	4 (2.8%)	2 (0.8%)	0.103
Painful sex	130 (36.3%)	79 (56.0%)	51 (23.5%)	<0.001
Obstetrics and Gynecology History				
Age of menarche, years				
8–10	3 (0.9%)	2 (1.5%)	1 (0.5%)	0.373
11–13	89 (25.3%)	36 (27.3%)	53 (24.1%)	
14–16	233 (66.2%)	87 (65.9%)	146 (66.4%)	
17–26	27 (7.7%)	7 (5.3%)	20 (9.1%)	
History of miscarriage	81 (20.1%)	42 (29.6%)	39 (14.9%)	<0.001

Variables	Total (n=404)	Case (n = 142)	Control (n = 262)	*P* *
History of stillbirth	14 (3.5%)	3 (2.1%)	11 (4.2%)	0.395
History of ectopic pregnancy	8 (2.0%)	6 (4.2%)	2 (0.8%)	0.025
Median no. of prior pregnancies (range)	2 (1–3)	1 (1–3)	2 (1–3)	<0.0001
Current Sexually Transmitted Infections (STIs)				
CT positive NAAT	17 (4.5%)	4 (2.8%)	13 (5.4%)	0.308
NG positive NAAT	9 (2.4%)	2 (1.4%)	7 (2.9%)	0.494
MG positive NAAT	26 (6.8%)	9 (6.4%)	17 (7.1%)	0.785
TV positive NAAT	13 (3.4%)	1 (0.7%)	12 (5.0%)	0.037
Any positive NAAT	59 (15.5%)	15 (10.6%)	44 (18.3%)	0.045
Multiple STIs	5 (1.5%)	1 (0.8%)	4 (2.0%)	0.652

*statistical analyses by Fisher exact test, $\chi 2$ test of independence, or Wilcoxon rank sum test as appropriate.

†"white collar" occupation referred to highly skilled occupations (such as teachers, lawyers, bankers, nurses, etc.), while "business" occupation referred to small business owners or retailers (such as sales agents, retailers, hairdressers, farmers, etc.)

CT, indicates *Chlamydia trachomatis*; NAAT, nucleic acid amplification test; NG, *Neisseria gonorrhoeae*; MG, *Mycoplasma genitalium*; TV, *Trichomonas vaginalis*; STIs, sexually transmitted infections.

Table 2.

Participant Characteristics by C*hlamydia trachomatis* (CT) Seropositivity Status

Variables	Total (n=404)	CT Seropositive (n = 372)	CT Seronegative (n = 32)	*P* *
Sociodemographics				
Median age, years (range)	29 (15–46)	29 (15–46)	31 (20–40)	0.796
Age, years				
15–24	95 (23.5%)	85 (22.9%)	10 (31.2%)	0.086
25–29	126 (31.2%)	122 (32.8%)	4 (12.5%)	
30–39	121 (30.0%)	109 (29.3%)	12 (37.5%)	
40–46	62 (15.4%)	56 (15.1%)	6 (18.8%)	
Occupation†				
White Collar	103 (25.5%)	90 (24.2%)	13 (40.6%)	0.107
Business	182 (45.1%)	171 (46.0%)	11 (34.4%)	
None	74 (18.3%)	71 (19.1%)	3 (9.4%)	
Student	45 (11.1%)	40 (10.8%)	5 (15.6%)	
Marital Status				
Single, Divorced or Widowed	137 (33.9%)	122 (32.8%)	15 (46.9%)	0.106
Married	267 (66.1%)	250 (67.2%)	17 (53.1%)	
Education				
None or Primary	73 (18.1%)	69 (18.6%)	4 (12.5%)	0.393
Secondary, High School or Vocational	231 (57.2%)	214 (57.5%)	17 (53.1%)	
University	100 (24.8%)	89 (23.9%)	11 (34.4%)	
Sexual History				
Age of sexual debut, years				
<14	14 (3.8%)	12 (3.6%)	2 (6.5%)	0.030
14–19	273 (74.2%)	256 (76.0%)	17 (54.8%)	
≥20	81 (22.0%)	69 (20.5%)	12 (38.7%)	
Lifetime sex partners				
1–5	304 (85.4%)	275 (84.4%)	29 (96.7%)	0.100
≥5	52 (14.6%)	51 (15.6%)	1 (3.3%)	
Currently more than one sexual partner	6 (1.5%)	5 (1.3%)	1 (3.1%)	0.392
Painful sex	130 (36.3%)	120 (36.6%)	10 (33.3%)	0.723
Obstetrics and Gynecology History				
Age of menarche, years				
8–10	3 (0.9%)	2 (0.6%)	1 (3.3%)	0.114
11–13	89 (25.3%)	80 (24.8%)	9 (30.0)	
14–16	233 (66.2%)	213 (66.2%)	20 (66.7%)	
17–26	27 (7.7%)	27 (8.4%)	0 (0%)	
History of miscarriage	81 (20.1%)	69 (18.6%)	12 (37.5%)	0.010

Variables	Total (n=404)	CT Seropositive (n = 372)	CT Seronegative (n = 32)	*P* *
History of stillbirth	14 (3.5%)	14 (3.8%)	0 (0%)	0.615
History of ectopic pregnancy	8 (2.0%)	7 (1.9%)	1 (3.1%)	0.486
Median no. of prior pregnancies (range)	2 (1–3)	2 (1–3)	2 (1–3)	0.571
Duration of infertility, years‡				
1–5	98 (69.0%)	88 (67.2%)	10 (90.9%)	0.173
>5	44 (31.0%)	43 (32.8%)	1 (9.1%)	
Current Sexually Transmitted Infections (STIs)				
CT positive NAAT	17 (4.5%)	16 (4.6%)	1 (3.6%)	1.000
NG positive NAAT	9 (2.4%)	9 (2.6%)	0 (0%)	1.000
MG positive NAAT	26 (6.8%)	24 (6.8%)	2 (7.1%)	1.000
TV positive NAAT	13 (3.4%)	13 (3.7%)	0 (0%)	0.611
Any positive NAAT	59 (15.5%)	56 (15.9%)	3 (10.7%)	0.595
Multiple STIs	5 (1.5%)	5 (1.7%)	0 (0%)	1.000

*Statistical analyses by Fisher exact test, $\chi 2$ test of independence, or Wilcoxon rank sum test as appropriate.

†"white collar" occupation referred to highly skilled occupations (such as teachers, lawyers, bankers, nurses, etc.), while "business" occupation referred to small business owners or retailers (such as sales agents, retailers, hairdressers, farmers, etc.)

‡Analyses limited to cases (N = 142).

CT, indicates *Chlamydia trachomatis*; NAAT, nucleic acid amplification test; NG, *Neisseria gonorrhoeae*; MG, *Mycoplasma genitalium*; TV, *Trichomonas vaginalis*; STIs, sexually transmitted infections.