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MAJOR ARTICLE

Prevalence of *Chlamydia trachomatis* Among Pregnant Women, Gynecology Clinic Attendees, and Subfertile Women in Guangdong, China: A Cross-sectional Survey

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Background. *Chlamydia trachomatis* (CT) is a major cause of infertility and adverse birth outcomes, but its epidemiology among childbearing-age women remains unclear in China. This study investigated the prevalence of CT and associated factors among Chinese women aged 16–44 years who were either (1) pregnant, (2) attending gynecology clinics, or (3) subfertile.

Methods. We conducted a cross-sectional survey and recruited participants from obstetrics, gynecology, and infertility clinics in Guangdong between March and December 2019. We collected information on individuals' sociodemographic characteristics, previous medical conditions, and sexual behaviors. First-pass urine and cervical swabs were tested using nucleic acid amplification testing. We calculated the prevalence in each population and subgroup by age, education, and age at first sex. Multivariable binomial regression models were used to identify factors associated with CT.

Results. We recruited 881 pregnant women, 595 gynecology clinic attendees, and 254 subfertile women. The prevalence of CT was 6.7% (95% CI, 5.2%–8.5%), 8.2% (95% CI, 6.2%–10.7%), and 5.9% (95% CI, 3.5%–9.3%) for the above 3 populations, respectively. The subgroup-specific prevalence was highest among those who first had sex before age 25 years and older pregnant women (>35 years). The proportion of asymptomatic CT was 84.8%, 40.0%, and 60.0% among pregnant women, gynecology clinic attendees, and subfertile women, respectively. Age at first sex (<25 years), multipara, and ever having more than 1 partner increased the risk of CT.

Conclusions. Childbearing-age women in China have a high prevalence of CT. As most women with CT were asymptomatic, more optimal prevention strategies are urgently needed in China.

Keywords. *Chlamydia trachomatis*; epidemiology; pregnancy; prevalence; STI.

Chlamydia trachomatis (CT) is the most prevalent bacterial sexually transmitted infection (STI) in the world and is an established cause of tubal factor infertility, ectopic pregnancy, preterm birth, stillbirth, and neonatal conjunctivitis and pneumonia [1, 2]. A global estimate showed the total cost of sequelae per case of untreated CT ranging from £37 to £412 [3]. In addition to serious reproductive health morbidity, CT may facilitate horizontal transmission of HIV [4]. In addition to the serious complications, the frequently asymptomatic nature of CT in women is well established, and nearly 30%–70% of infected women are not diagnosed. So, early detection and treatment of CT in childbearing-age women has been regarded as a cost-effective strategy for improving the population's sexual health and reproductive health [5].

Understanding the prevalence of CT and its variation by region and population provides evidence for designing prevention strategies. In 2016, the World Health Organization (WHO) estimated that there were 127 million new cases of CT annually among people aged 15–49 years worldwide, with distinct regional variations [6]. The highest-prevalence estimates were reported in the regions of the Americas (7.0%; 95% CI, 5.8%–8.3%) and Africa (5.0%; 95% CI, 3.8%–6.6%). Similarly, studies from the United States, Australia, England, Germany,

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and other European countries [7–10] reported that the prevalence of CT varies by social demographics (eg, age, race/ethnicity, and education) and sexual behavior characteristics. The highest prevalence was usually reported among young sexually active women (age <25 years; eg, 3.1% in women aged 16–24 years and 1.5% in women aged 16–74 years in Britain between 2010 and 2012) [8], non-Hispanic Black women (5.2%; and 0.8% for non-Hispanic White women in the United States) [11], and high-risk populations (eg, 3.2% for female sex workers in 2017 in Australia) [12].

In China, data from all of the 105 national surveillance sites showed that the incidence rate of CT in women has increased from 52.74 cases per 100 000 persons in 2015 to 84.55 cases per 100 000 persons in 2019 [13]. Meanwhile, syndromic management of CT has been recommended as a prevention strategy, which limited treatment to symptomatic women and failed to identify most infected women [14]. In addition, 3 methods (nucleic acid amplification tests [NAATs], immunochromatographic tests [ICTs], and enzyme-linked immunosorbent assay) were used for *C. trachomatis* detection, and only 21.5% (341/1583) of laboratories used the NAAT method [15]. Considering the incomplete coverage of surveillance sites, the large proportion of asymptomatic infections, and the limited use of NAAT, we hypothesize that the prevalence of CT is underreported in China. There have been several publications about the epidemiology of CT in Chinese women of childbearing age in the past 2 decades [16–20]. A recent survey from Beijing, Zhejiang, Shenzhen, and Hunan showed that the prevalence of CT ranged from 4.7% to 10.2% in women. However, there are limited data on CT prevalence among pregnant and young women in China. The existing evidence base is inadequate to identify the priority areas and populations for targeting prevention strategies.

To understand the burden of CT among childbearing-age women, we conducted a cross-sectional survey in Guangdong province, China, to investigate the prevalence of CT and its risk factors among women who were pregnant, attendees of gynecology clinics, and women who were subfertile. These data will inform further development of CT prevention strategies in China.

METHODS

Study Design and Setting

We conducted a cross-sectional survey from March to November 2019 in Guangdong province, China. Guangdong province is located in Southern China and contains 21 major cities. It is 1 of the 4 provinces with mandatory reporting of CT cases and has the largest number of STI cases including syphilis and gonorrhea among 31 provinces in China [21]. For example, in 2019, the number of syphilis cases in China was 0.54 million, with Guangdong province reporting 62 760 cases.

Sampling Method

We first classified 21 cities as high, medium, and low level according to the previously reported incidence rates of CT in 2017 (Supplementary Table 1). Then, we randomly selected 1 prefecture city from each level to participate in the survey. We then recruited pregnant women, gynecology clinic attendees, and women attending infertility clinics from hospitals in these chosen cities to investigate patterns of CT. The list of participating hospitals and the details for the sampling process are shown in the Supplementary Data: Sampling Process, Supplementary Figures 1 and 2. We aimed for a minimum of 292 pregnant women, 528 gynecology clinic attendees, and 161 subfertile women to complete our survey (see the Supplementary Data for sample size calculations).

Participants Eligibility

Inclusion criteria were women 16–44 years of age who reported ever having had sex with men and who were willing to be tested for CT. We excluded women who used antibiotics in the preceding month, declined to join the study, or had an invalid sample for NAAT.

Survey

Study Questionnaire

Subjects provided informed consent at the time of enrollment. Those who agreed to participate in the study were referred to a separate and quiet room to fill out the questionnaire. Subjects completed the questionnaire regarding their sociodemographic characteristics, previous diagnoses of STIs (including syphilis, gonorrhea, genital herpes, condylomata acuminata, genital mycoplasma, or CT), chronic conditions, previous pelvic inflammation disease (PID), pregnancy history (eg, gravidity), current clinical symptoms, lifestyle, and sexual behaviors. The trained investigator would remind each participant that the previous STIs and other conditions should have been diagnosed by a clinician or laboratory result. All data collected from the questionnaire and laboratory results were anonymized.

Diagnostic Test

First-pass urine and cervical swabs were obtained from each participant from gynecology and infertility clinics. Considering ethics and safety, we only collected first-pass urine in pregnant women. Urine was self-collected by participants, and the cervical swabs were collected by the physicians. NAATs were performed on urine and cervical swabs for detection of *C. trachomatis* and *N. gonorrhoeae* (Cobas 48000 CT/NG Amplification/Detection Kit, Shanghai, China) in Guangdong Provincial Center for Skin Disease and STI Control. We chose test results according to the following criteria: (1) we excluded individuals from the study population when both urine and cervical swabs were invalid; (2) we chose a valid specimen as the final result when any 1 of the urine and cervical swabs was invalid; and (3) we chose urine as the final result when both urine and cervical swabs were valid, as it could be compared with the results of the pregnant women.

Statistical Analysis

Definitions of CT. CT cases were defined as women with a positive NAAT result. Asymptomatic cases were defined as women who did not report any of the following symptoms at enrollment time: lower abdominal pain, abnormal vaginal discharge, abnormal vaginal bleeding, dyspareunia or dysuria.

Previous STI was defined as those who were ever diagnosed with either syphilis, gonorrhea, genital herpes, condylomata acuminata, or genital mycoplasma. Chronic conditions included any 1 of heart disease, diabetes, kidney disease, or hepatic disease.

Statistical Analysis

We used OpenEpi Menu to calculate the sample size and R 3.4.1 for our statistical analyses. We used the chi-square test to compare the difference between categorical factors. The Fisher exact test was used as an alternative to the chi-square test when 1 or more of the cell counts in the cross-table was <5. We used multivariable logistic regression models to examine the association between current CT and potential risk factors. To decrease the effect of multiple collinearity, we separately included each potential factor in the model by adjusting for the known risk factors, such as age, education, and marital status [17]. We examined factors related to age at first sex, number of partners, previous PID diagnosis, previous diagnosis with chlamydia, ever engaged in smoking in their lifetime, ever engaged in alcohol use in their lifetime, and gravidity.

Patient Consent Statement

Each patient's written consent was obtained. This study was approved by Ethical Committee at the Dermatology Hospital of Southern Medical University (Approval Number: GDDGLS-20190312).

RESULTS

Sociodemographic and Clinical Characteristics of the Study Population

Overall, 1730 participants, including 881 (50.9%) pregnant women from obstetrics clinics, 595 (34.4%) gynecology clinic attendees, and 254 (14.7%) subfertile women from infertility clinics, were recruited. The characteristics of each study population are shown in Table 1. The mean age was 30.2 ± 5.4 years, and the mean age of first sexual intercourse was 22.0 ± 3.5 years. Of participants, 7.1% were diagnosed as having a current infection of CT, while 0.7% reported a previous diagnosis of CT, 2.0% reported being diagnosed with a previous STI, and 6.1% reported a previous diagnosis of PID. The proportion with a previous CT diagnosis was much higher in subfertile women (2.4%) compared with pregnant women (0.3%; P = .01). Forty-one percent of women attending gynecology clinics reported having >1 partner in the last 12 months, and 8.7% reported having a casual sex partner in the last 12 months, while 29.7% did not use a condom when they had sex with their casual sex partners.

Chlamydia trachomatis Prevalence

As Table 2 shows, CT prevalence was 6.7% (95% CI, 5.2%–8.5%) in pregnant women, 8.2% (95% CI, 6.2%–10.6%) in gynecology clinic attendees, and 5.9% (95% CI, 3.5%–9.3%) in subfertile women. The differences among these 3 populations were not statistically significant. Additionally, there was no one with a co-infection with *Neisseria gonorrhoeae*.

Chlamydia trachomatis Prevalence by Subgroup

For age-specific CT prevalence in Table 2, the highest estimates occurred in pregnant women aged 36–44 years (13.5%; 95% CI, 7.9%–21.1%), gynecology clinic attendees aged 18–20 years (23.8%; 95% CI, 8.2%–47.2%), and subfertile women aged 21–25 years (7.3%; 95% CI, 1.5%–19.9%).

For education-specific chlamydia prevalence, the highest estimates occurred in pregnant women with an education level of high school or less (8.0%; 95% CI, 5.6%–11.1%) and in gynecology clinic attendees (25.0%) and subfertile women (7.8%; 95% CI, 3.7%–14.4%) with an education level of a Master's degree or higher. The differences between subgroups in each population were not statistically significant.

Women who first had sex at a younger age (<25 years) had the highest CT prevalence. In particular, among pregnant women and gynecology clinic attendees, the prevalence rates of CT were 22.1% (95% CI, 15.6%–30.4%) and 11.3% (95% CI, 5.6%–17.0%), respectively.

Proportion of Asymptomatic Infection

Among women with CT, 62.0% were asymptomatic. Pregnant women had the largest proportion of asymptomatic cases (84.8%, 39/46). Forty percent (18/45) of gynecology clinic attendees and 60.0% (9/15) of subfertile women were asymptomatic. The difference in asymptomatic cases was significant between pregnant women and gynecology clinic attendees (P < .05).

Factors Associated With *Chlamydia trachomatis*

As Table 3 shows, earlier age of first sex (<25 years) was positively associated with CT ($PR_{\text{obstetrics clinics}}$, 2.9; 95% CI, 1.2–9.1; $PR_{\text{infertility clinics}}$, 7.5; 95% CI, 1.5–137.4). Besides, multiparous women had a higher risk of CT among pregnant women (PR, 2.3; 95% CI, 1.1–5.6), and gynecology clinic attendees who had >2 partners

Table 1. Characteristics of Women Recruited in the Cross-sectional Study in Guangdong, China, 2018–2019 (n = 1730)

	Obstetrics Clinic (n = 881)		Gynecology Clinic (n = 595)		Infertility Clinic (n = 254)	
	No.	%	No.	%	No.	%
Women with CT	60	6.81	48	8.07	15	5.91
Age						
16–20 y	23	2.61	21	3.53	0	0
21–25 y	167n	18.96	74	12.44	41	16.14
26–30 y	347	39.39	164	27.56	115	45.28
31–35 y	233	26.45	171	28.74	70	27.56
36–44 y	104	11.8	158	26.55	29	11.42
Missing data	7	0.79	7	1.18	-	-
Education						
High school or less	376	42.68	395	66.39	50	19.69
Bachelor's	353	40.07	184	30.92	102	40.16
Master's or higher	146	16.57	4	0.67	102	40.16
Missing data	6	0.68	12	2.02	-	-
Marital status						
Unmarried	68	7.72	108	18.15	23	9.06
Married/living with partner	803	91.15	456	76.64	231	90.94
Divorced/widowed/separated	4	0.45	23	3.87	0	0
Missing data	6	0.68	8	1.34	-	-
Family income per month (RMB)						
≤10 000	639	72.53	563	94.62	238	93.7
10 001–30 000	170	19.3	10	1.68	16	6.3
>30 000	12	1.36	10	1.68	0	0
Missing data	60	6.81	12	2.02	-	-
Age at first sex						
<25 y	131	14.87	133	5.55	49	19.22
≥25 y	443	50.28	424	71.26	206	80.78
Missing data	306	34.73	41	6.89	-	-
Previous CT						
Yes	2	0.23	4	0.67	6	2.36
No	596	99.67	591	99.33	248	97.64
Previous PID						
Yes	16	2.68	45	7.56	44	17.32
No	582	97.32	550	92.44	211	83.07
Previous STIs						
Yes	4	0.67	24	4.03	6	2.36
No	594	99.33	571	95.97	249	98.03
Symptomatic current CT						
Yes	7	11.86	17	34.69	6	40.00
No	39	66.10	18	36.73	9	60.00
Missing data	13	22.03	14	28.58	0	-
Ever having >1 sex partner[a]						
Yes	-	-	244	41.01	22	8.67
No	-	-	286	48.07	231	90.94
Missing data	-	-	65	10.92	0	0
Ever having casual sex partner(s)[a]						
Yes	-	-	299	50.25	21	8.27
No	-	-	210	35.29	234	92.13
Missing data	-	-	86	14.45	0	0
Frequency of condom use[b]						
Always	42	13.09	16	70.28	3	14.29
Sometimes	55	17.13	44	18.40	7	33.33
Never	224	69.78	27	11.30	11	52.38

Abbreviations: CT, *Chlamydia trachomatis*; PID, pelvic inflammation disease; RMB, Ren Min Bi; STIs, sexually transmitted infections, including syphilis, gonorrhea, genital herpes, condylomata acuminata, or genital mycoplasma.

[b]For gynecology clinic attendees, this item means the number of sex partners in a lifetime; for subfertile women, this item means the number of sex partners in preceding 12 months.

[c]For pregnant women, the frequency of condom use was measured after pregnancy; only 321 women were engaged in sex after pregnancy. For gynecology clinic attendees and subfertile women, this item means the frequency of condom use during sex with a casual partner.

Table 2. Prevalence of *Chlamydia trachomatis* Among Women Aged 16–44 Years in Guangdong, China

Subgroups	No. of CT Cases	Prevalence, %		*P* Value
		Rate	95% CI	
Obstetrics clinics	60	6.70	5.20–8.50	
Age				.02
16–20 y	1	4.35	0.11–21.95	
21–25 y	16	9.58	5.78–14.78	
26–30 y	14	4.03	2.31–6.52	
31–35 y	15	6.44	3.79–10.17	
36–44 y	14	13.46	7.88–21.06	
Education				.57
High school or less	29	8.38	5.79–11.66	
Bachelor's	20	5.67	3.59–8.46	
Master's or higher	10	6.85	3.53–11.87	
Age at first sex				<.001
<25 y	29	22.14	15.55–30.40	
≥25 y	14	3.16	1.55–4.96	
Gynecology clinic	48	8.20	6.20–10.60	
Age				.11
16–20 y	5	23.81	8.22–47.14	
21–25 y	7	9.46	3.89–18.52	
26–30 y	16	9.76	5.88–15.04	
31–35 y	12	7.01	3.86–11.62	
36–44 y	8	5.06	2.38–9.39	
Education				.29
High school or less	30	7.59	5.28–10.53	
Bachelor's	17	9.24	5.66–14.1	
Master's or higher	1	25.0	1.25–75.77	
Age at first sex				<.001
<25 y	15	11.28	5.58–16.99	
≥25 y	30	7.08	4.54–9.61	
Infertility clinics	15	5.90	3.50–9.30	
Age				
16–20 y	0	0	-	.88
21–25 y	3	7.32	1.54–19.92	
26–30 y	7	6.09	2.70–11.67	
31–35 y	5	7.25	2.40–16.11	
36–44 y	0	0	-	
Education				
High school or less	1	2.04	0.05–10.85	.45
Bachelor's	6	5.88	2.19–12.36	
Master's or higher	8	7.84	3.71–14.35	
Age at first sex				
<25 y	7	14.29	3.70–24.9	.27
≥25 y	16	7.77	3.96–11.57	

Abbreviation: CT, Chlamydia trachomatis.

in past 12 months had a greater odds ratio of CT (*PR*, 1.9; 95% CI, 1.2–2.8).

DISCUSSION

Our study estimated CT prevalence among women of reproductive age in Guangdong Province, China. We extend the existing literature by estimating the prevalence in pregnant women, gynecology clinic attendees, and infertility clinic attendees. In addition, we disaggregated CT prevalence according to known risk factors, such as age and age at first sex. These findings provided clues to identify the priority population and clinic for CT prevention.

Our study reveals a large hidden disease burden of undiagnosed CT among Chinese women. Compared with the CT prevalence in countries such as United States (7.4% in pregnant women during 2014–2017) [22] and low- and middle-income countries in Asia (0.8% in 2012–2015) [23], our study population had a higher prevalence: 6.7% for pregnant women, 8.2% for gynecology clinic attendees, and 5.9% for infertility clinic

Table 3. Factors Associated With *Chlamydia trachomatis* Among Women Aged 16–44 Years in Guangdong, China

	Univariate Analysis		Multivariable Analysis	
Variables	Crude *PR*	95% CI	Adjusted *PR*	95% CI
Obstetrics clinics				
Age at first sex				
≥25 y	Ref.	-	Ref.	-
<25 y	2.14	(0.95–5.75)	2.94*	(1.15–9.11)
Previous PID	0.81	(0.04–4.16)	0.85	(0.05–4.40)
Ever engaged in smoking	2.82	(1.91–11.37)	2.77	(0.41–11.47)
Ever engaged in alcohol use	1.36	(0.50–3.15)	1.35	0.49–3.16
Gravidity				
0	Ref.	-	Ref.	-
≥1	1.88	0.94–4.11	2.34*	1.06–5.61
Gynecology clinics				
Age at first sex				
≥25 y	Ref.	-	Ref.	-
<25 y	2.74*	(1.08–9.27)	2.08	0.78–7.27
No. of partners in past 12 mo				
1	Ref.	-	Ref.	-
≥2	1.93***	(1.30–2.84)	1.85**	(1.23–2.75)
Previous PID	1.26	(0.51–3.14)	1.43	0.58–3.75
Previous CT	5.80	(0.27–61.66)	6.51	(0.22–199.69)
Ever engaged in smoking	2.25	(0.76–5.38)	1.83	(0.60–4.45)
Ever engaged in alcohol use	1.64***	(1.15–2.34)	1.28	0.86–1.91
Gravidity				
0	Ref.	-	Ref.	-
≥1	1.04	(0.61–2.15)	2.04	(0.94–5.04)
Infertility clinics				
Age at first sex				
≥25 y	Ref.	-	Ref.	-
<25 y	7.17	(1.45–129.7)	7.48*	(1.45–137.37)
No. of partners in past 12 mo				
1	Ref.	-	Ref.	-
≥2	1.05	(0.39–2.12)	1.21	(0.43–2.63)
Previous PID	0.43	(0.07–1.55)	0.35	(0.05–1.26)
Previous CT	2.06	(0.11–13.57)	2.83	(0.14–22.39)
Ever engaged in smoking	1.50	(0.09–7.22)	2.29	(0.12–14.00)
Ever engaged in alcohol use	1.44	(0.48–3.57)	1.25	(0.40–3.21)
Gravidity				
0	Ref.	-	Ref.	-
≥1	0.76	(0.32–1.90)	0.59	(0.24–1.55)

Abbreviations: CT, *Chlamydia trachomatis*; PID, pelvic inflammation disease; *PR*, prevalence ratio.
**P* < .05; ***P* < .01; ****P* < .001.

attendees. We also note a relatively high prevalence in women from Shenzhen (10.1% in sexual and reproductive health clinics in 2018) [24], Taizhou (10.2% in gynecology outpatients during 2013–2018), and Beijing (5.9% in outpatient clinic attendees during 2013–2016) [16]. The lower prevalence for women attending infertility clinics may be explained by the following reasons: (a) we included all subfertile women, and ~30% of them suffered tubal infertility; (b) we used NAAT to test chlamydia, which measures current infection status and not past infection; a study on CT and infertility showed that a past CT infection was a key determinant of tubal infertility [25]; and (c) past chlamydia infection has ascended to and been recurrent in uteran tubal, and other remote sites in infertile women, but it cannot be detected in urine or cervical swabs. Besides, we did not detect a single case of *Neisseria gonorrhoeae*. This may be explained by the following: (a) the effective prevention for *Neisseria gonorrhoeae* sharply reduced the incidence rate so that we could not capture the cases [26]; and (b) we recruited participants from obstetric, gynecology, and infertility clinics. The prevalence of STIs was low in the 3 populations. Anyway, the above figures highlight the urgent need to implement CT prevention among women in China.

An integrated CT prevention and control program including screening, behavioral interventions, and education is needed. We found that only a minority of women had ever been tested for CT and knew their infection status; only 0.69% of participants reported a history of infection. Among the 3 populations, the gynecology clinic attendees had the highest prevalence of CT. Although we used a broad definition of symptomatic case, we still found the proportion of asymptomatic cases was nearly 85% among pregnant women. Our finding was higher than the 34.2% rate from Shenzhen [20] and implied an urgent need to explore optimal routine CT screening strategies in antenatal care services. Evidence from Australia shows that screening for CT among young pregnant women (<25 years) is cost-effective [5]. In addition, we found that nearly 30% of gynecology clinic attendees had engaged in condomless sex in the past 12 months, which may indicate the reasons behind the high CT prevalence rate in Chinese women. So, there is a key role for behavioral interventions and sexual health education in these subpopulations of women to prevent *C. trachomatis* acquisition.

Furthermore, our findings suggest the need for targeted testing of both young women (<25 years) and older pregnant women (>35 years) in the design of CT prevention strategies. Consistent with the current screening criteria for the target population (<25 years, or ≥25 years with high-risk behaviors) [27–29], we found the younger subgroups to have a high prevalence. Interestingly, we also observed that the highest prevalence occurred in pregnant women aged >35 years. This may be explained by the initiation of the 2-child policy in the past few years, as our results indicate that women who have 2 or more pregnancies are more likely to have CT (a*PR*, 2.34; 95% CI, 1.06–6.51). Therefore, in the future studies, we suggest that others confirm the high CT prevalence in pregnant women aged >35 years and identify the optimal target population for CT prevention strategies.

Our study has several limitations. First, this study is a hospital-based survey, which may have overestimated CT prevalence due to differences in sexual and health-seeking behaviors of hospital clinic attendees compared with the general population. Second, we collected information on sexual history, previous CT, and sexual behavior using self-reports, so recall and social desirability bias cannot be excluded. Despite these limitations, the high prevalence of CT and large proportion of asymptomatic cases emphasize the urgent need to design specific CT prevention strategies in these subpopulations. Further, these results reiterate the need for more research and programs to provide comprehensive interventions to improve knowledge of safer sex strategies to complement CT prevention programs.

CONCLUSIONS

Women of childbearing age have a relatively high prevalence of CT in China, with 40%–80% being asymptomatic. To control CT, the optimal preventive strategy to detect asymptomatic CT in antenatal, gynecology, and infertility clinics is urgently needed in China.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Data availability. Data available by contacting the corresponding author.

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