

## Brief Communication



# Antimicrobial Resistance for *Chlamydia Trachomatis* Genital Infection during Pregnancy in Japan

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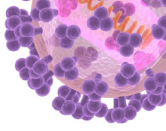
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## ABSTRACT

The current study examined the antimicrobial resistance of *Chlamydia trachomatis* (CT) genital infection during pregnancy in Japan. We requested 2,146 obstetrical facilities that are members of Japan Association of Obstetricians and Gynecologists to provide information of CT screening tests and antimicrobial resistance in pregnant women between April 2020 and March 2021. The prevalence of CT genital infection in Japan was 2.1%. The antimicrobial resistance was recognized in 2.0 and 2.4% of the cases using azithromycin and clarithromycin, respectively. There were no significant differences in the antimicrobial resistance rate between the 2 analogues ( $P = 0.28$ ). In Japan, azithromycin and clarithromycin have effectively treated genital CT infections during pregnancy.

**Keywords:** Antimicrobial resistance; *Chlamydia trachomatis*; Azithromycin; Clarithromycin; Japan

Genital *Chlamydia trachomatis* (CT) is the most commonly sexually transmitted infection reported in developed countries. Based on our previous observation in 2014 [1], the prevalence of CT genital infection in pregnant women was 2.3% in Japan. In Japan, pregnant women are routinely tested for genital CT with the Japanese public funds, and treatment with a single dose of oral azithromycin (1.0 g) or oral clarithromycin (200 mg × 2/day, 7 days) is required in pregnant women with CT genital infection for the prevention of neonatal CT infection according to the guidelines for obstetrical practice in Japan [2]. The total cost of oral azithromycin and oral clarithromycin are 280 - 820 and 290 - 610 yen (about 110 yen = 1 US dollar), respectively. The presence of CT genital infection is diagnosed when CT is detected using nucleic acid amplification tests, nucleic acid hybridization tests, an enzyme immunoassay, or culture methods in specimens obtained from the uterine cervix [2]. Earlier trials in 2002 - 2010 had indicated that both treatments are more than 95% effective [3]; however, an observation in 2012 by Handsfield [4] has strongly suggested that treatment failure may occur in more than 5% patients. One of the reasons for the increase in treatment failure with azithromycin has been suggested to be the impossibility of the detect of small numbers of persistent CT [4]. However, the review of the evidence for treatment failure will be needed to deny the necessity to modify the treatment regimes. Azithromycin and


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**Ethics statement**

This study was conducted after receiving approval from the ethics committee of the Japan Association of Obstetricians and Gynecologists (JAOG) (IRB No. 202103). And patient informed consent was waived.

**Conflict of Interest**

No conflict of interest.

**Data Availability**

The authors declare that data supporting the findings of this study are available within the article.

**Author Contributions**

Conceptualization: SS, KK, TK. Data curation: SS. Formal analysis: SS, SH, YS, AS. Investigation: SS, SH, YS, AS. Writing - original draft: SS. Writing - review & editing: SH, YS, AS, KK, TK.

clarithromycin are old erythromycin analogues [5]. Both azithromycin and clarithromycin are equivalent to standard oral therapies against respiratory tract and soft tissue infection. To date, any significant data indicating the difference in the therapeutic effect on CT genital infection between the 2 analogues have not been reported [2, 5]. Based on the backgrounds, the current study examined the evidence for treatment failure of CT genital infection during pregnancy, considers whether we need to modify current treatment regimes in Japan.

This study was conducted after receiving approval from the ethics committee of the Japan Association of Obstetricians and Gynecologists (JAOG).

On August 2021, we requested 2,146 obstetrical facilities that are members of the JAOG to provide information of CT screening tests and antimicrobial resistance in pregnant women between April 2020 and March 2021. In this study, the presence of antimicrobial resistance was determined if CT is detected again 3 - 4 weeks after the first or second completed oral dose based on the guideline for obstetrical practice in Japan [2].

Data are presented as number (%). For statistical analysis, the  $\chi^2$  test for categorical variables was used. Differences with  $P < 0.05$  were considered significant.

A total of 1,459 (67.8%) of 2,146 obstetrical facilities responded with possible statistical analysis information on a total of approximately 590,000 deliveries. There were 12,113 women (2.1%) with CT genital infection. As the first-line antibiotics, azithromycin and clarithromycin were used in 10,438 (86.2%) and 1,519 (12.5%), respectively. The antimicrobial resistance was recognized in 210 (2.0%) and 37 (2.4%) of the cases using azithromycin and clarithromycin, respectively. There were no significant differences in the antimicrobial resistance rate between the 2 analogues by the  $\chi^2$  test ( $P = 0.28$ ). Three-4 weeks after taking the second-line antibiotics, CT was not detected in any cases.

In the current study, the prevalence of CT genital infection during pregnancy was almost similar to that in our previous same study (2.3%) [1]. In this study, since there seemed to be no cases with the problems in completing the oral medication or no cases of persistent CT after changing antibiotics, antimicrobial resistance may be the only reason for treatment failure. The rate of antimicrobial resistance of CT genital infection to azithromycin and clarithromycin was both about 2.0%. Fortunately, CT was not detected in any cases 3 - 4 weeks after taking the second-line antibiotics.

In this study, we could not find the significant difference in the therapeutic effect for CT genital infection between the 2 analogues. In addition, the rate of treatment failure of the 2 analogues was lower than expected [3, 4]. In addition, there were no cases of ineffectiveness in both analogues. Therefore, there seems to be no need to modify our current treatment regimes in Japan to prevent neonatal CT infection [2].

Around 2,000 when azithromycin was released, some patients have been reported to give up taking medication due to the side effects such as nausea and stomach pain [6]. However, information on the side effects has been fully enlightened, and guidance such as taking medicine before going to bed has come to be given. In this study, there were no reports that the treatment was not completed. In addition, it has been common to be instructed not to have sexual intercourse until treatment is complete for genital CT infections; however, the confirmation of unsexual intercourse was left to the individual doctor.

The above may be the limitations of the current study; however, in any case, azithromycin and clarithromycin effectively treated about 98% of genital CT infections. About 2.0% of cases in which each antibiotic was ineffective could be treated with another antibiotic. Because there is no difference in the effectiveness of the 2 antibiotics, azithromycin may be a priority antibiotic with less burden on the patient because it is administered only once. The convenient dosing schedule of azithromycin may improve patient compliance.

We understand there are some serious limitations except the small sample size of this study. Based on the Japanese guideline [2], CT genital infection has been diagnosed when CT is detected using nucleic acid amplification tests, nucleic acid hybridization tests, an enzyme immunoassay, or culture methods in specimens obtained from the uterine cervix. However, the difference in the detection rate depending on these methods has not been well examined. The timing of the CT test during pregnancy has not also been determined. In addition, the partner of any woman infected with CT had been recommended to undergo a screening test for CT infection to prevent re-infection of the woman; however, it has not been examined whether the screening is thorough [2].

In Japan, azithromycin and clarithromycin have effectively treated about 98% of genital CT infections during pregnancy. There seems to be no need to modify our current treatment regimes in Japan to prevent neonatal CT infection.

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