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Research Article

Antimicrobial Susceptibility Patterns in *Neisseria gonorrhoeae* Isolated from South African Pregnant Women

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Background. *Neisseria gonorrhoeae*, a sexually transmitted infection, is associated with adverse pregnancy and neonatal outcomes. Emerging resistance towards various antibiotics has been observed globally. However, there is a lack of data on antimicrobial susceptibility patterns in *N. gonorrhoeae* isolated from pregnant women in our setting. This study fills in this gap in the literature. *Methods*. The study population included pregnant women, recruited from the antenatal clinic of the King Edward VIII hospital (KEH) in Durban. Endocervical swabs were obtained from 307 women. The swab was placed in Amies Charcoal media for culture assessments. Pure isolates of *N. gonorrhoeae* were subjected to antimicrobial susceptibility testing using the Etest™ method. The MIC values were assessed in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2019) breakpoints. *Results*. The prevalence of *N. gonorrhoeae* by culture was 1.9%. High MIC values to penicillin G (12-64 mg/L) indicating a resistant phenotype were observed for all isolates tested, with 50% of the isolates displaying complete resistance. Isolates with intermediate (1 mg/L) and resistance (1.9-32 mg/L) profiles to tetracycline were observed. Resistance to ciprofloxacin (1.16-3 mg/L) was also observed. Isolates displayed either dual or triple resistance to penicillin G, tetracycline, or ciprofloxacin. All isolates showed susceptibility to spectinomycin (>64 mg/L), azithromycin (1 mg/L), ceftriaxone (>0.125 mg/L), and cefixime (>0.125 mg/L). *Conclusion*. Despite lack of resistance to ceftriaxone and azithromycin, continuous surveillance for emerging patterns of resistance to these antibiotics is needed since they form part of the treatment guidelines.

1. Introduction

Neisseria gonorrhoeae is the second most prevalent bacterial sexually transmitted infection (STI) and is a major cause of mortality and morbidity [1]. A global STI surveillance in 2018 was conducted by the World Health Organization (WHO) and revealed an estimated 87 million new gonorrhoea infections globally during 2016, with an incidence of 20 cases per 1000 population (uncertainty interval 14–28) in women [2]. A study conducted in South Africa and Zimbabwe reported an overall prevalence of 0.7% for *N. gonorrhoeae* infections in women from the general population [3]. Other studies conducted in South Africa have reported prevalence rates for *N. gonorrhoeae* from 3%-11% in women [1, 4, 5]. A study conducted exclusively on pregnant women reported a prevalence of 1.3% for *N. gonorrhoeae* [6].

The worldwide clinical management of *N. gonorrhoeae* infections is becoming increasingly challenging due to antimicrobial resistance (AMR) to various classes of available antibiotic therapy [7]. Untreated *N. gonorrhoeae* infections are associated with a range of adverse pregnancy outcomes such as conjunctivitis, foetal growth retardation, spontaneous abortion, stillbirth, prematurity, low birth weight, postpartum endometritis, and increased risk of Human

Immunodeficiency Virus (HIV) transmission from mother to child during birth [1, 8–18]. Therefore, it is highly critical that pregnant women undergo antimicrobial sensitivity testing for *N. gonorrhoeae* in order to initiate proper patient management and thus prevent these adverse pregnancy outcomes.

The withdrawal of sulphonamides, penicillins, earlier cephalosporins, tetracyclines, macrolides, and fluoroquinolones led to limited treatment options for this infection [14, 19, 20]. In most settings worldwide, ceftriaxone is the last remaining option for empirical first-line antimicrobial monotherapy [14]. However, decreasing susceptibility of *N. gonorrhoeae* to ceftriaxone has been reported with the proportion of resistance to ceftriaxone varying extensively, from 1.3% to 55.8% [21].

Ceftriaxone was the last remaining option for empirical first-line antimicrobial monotherapy [14]. South Africa was in accordance with the recommendation made by the WHO which advocated for the replacement of the first-line treatment with oral cefixime to a single injectable dose (250 mg) of ceftriaxone in 2014 [18]. Treatment failures of ceftriaxone monotherapy led to the WHO recommendation of administering dual antimicrobial therapy with the combination of ceftriaxone (250 mg) and azithromycin (1 g stat) [11, 13, 22, 23]. However, decreasing susceptibility of *N. gonorrhoeae* to ceftriaxone has been reported with the proportion of resistance to ceftriaxone varying extensively, from 1.3% to 55.8% [21]. In addition, resistance to azithromycin is already prevalent in many settings [14]. Therefore, dual antimicrobial therapy cannot ensure long-term effectiveness.

Currently, there is limited data on *N. gonorrhoeae* susceptibility patterns in pregnant populations from KwaZulu-Natal (KZN) in South Africa. This study provides data on susceptibility patterns to penicillin G, tetracycline, ciprofloxacin, azithromycin, spectinomycin, cefixime, and ceftriaxone in pregnant women from our setting.

2. Materials and Methods

2.1. Ethical Statement. Full ethics approval for this study was granted by the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal (UKZN) (BE355/18).

2.2. Study Setting and Population. The study population included pregnant women, who were 18 years and older, willing to provide written informed consent, willing to provide biological samples (endocervical swabs), and willing to provide data on their demographics, sexual behaviour, and clinical history. The study population was recruited from the antenatal clinic of the King Edward VIII hospital (KEH) in Durban, South Africa, from November 2018 to July 2019. Due to the nature of the sample collection, we had a 50% refusal rate during screening. Eventually, the number of women enrolled in this study was 307 participants.

2.3. Sample Collection and Processing. Each consenting woman was subjected to a clinical examination by a gynaecologist during which endocervical swab samples were collected. The swab was placed in Amies Charcoal transport media (LASEC, South Africa) immediately after collection. The swab was processed within 4 hours after collection at the Clinical Medicine Laboratory at the University of KwaZulu-Natal.

2.4. Culture Detection of N. gonorrhoeae. Upon arrival at the laboratory, the Amies swabs were streaked onto New York City Agar plates and incubated for 24-48 hours in the presence of 5% CO_2. After incubation, suspected colonies were subcultured onto chocolate agar plates and incubated for a further 24 hours in the presence of 5% CO_2. To confirm the identity of the isolates, gram staining, oxidase, catalase, and superoxol tests were conducted.

2.5. Detection of Antimicrobial Susceptibility and Resistance Profiles by the Etest™ Method. Culture confirmed isolates were subjected to antimicrobial susceptibility testing. A 0.5 McFarland (Thermo Fisher Scientific, United States) inoculum was prepared using each of the *N. gonorrhoeae* culture-positive isolates in 1 mL Mueller-Hinton Broth (LASEC, South Africa). The Etest™ method (BioMérieux, France) was conducted on chocolate agar plates to determine the minimum inhibitory concentrations (MICs) (mg/L) of azithromycin (0.016–256), cefixime and ceftriaxone (0.002–32), ciprofloxacin (0.002–32), penicillin G (0.016–256), tetracycline (0.016–256), and spectinomycin (0.064–1024). The WHO kindly provided strains, G, W, X, Y, and Z for use as positive controls. The MIC values were assessed in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2019) breakpoints.

2.6. Data Analysis. The data analysis was conducted using R Statistical computing software (version 3.6.3), a freely available software. Age, the only numerical variable, was summarised to show the minimum, maximum, and quartiles. The categorical characteristics were described using counts and percentage frequencies. The results were stratified by infection status of *N. gonorrhoeae*, that is, either negative or positive. Due to the skewness of the age distribution, the median comparison between the two groups was conducted using Wilcoxon rank sum test. On the other hand, associations in cross-tabulations were tested using either Fisher's exact test for cross-tabulations involving counts less than 5 or chi-square test, otherwise. All the tests were conducted at 5% level of significance.

3. Results

3.1. Overview and Prevalence Estimates of the Study Population. Of the total 307 women who participated in this study, 6/307 isolates were confirmed to be *N. gonorrhoeae* by culture. The prevalence of *N. gonorrhoeae* by culture was 1.9%. There was no significant association between demographic, behavioural, and clinical factors and infection status (Table 1). Despite the lack of significance, a large proportion of the study women (80.1%) did not present with symptoms of abnormal vaginal discharge, had reported having between 2 and 4 lifetime sex partners (61.2%), were unmarried

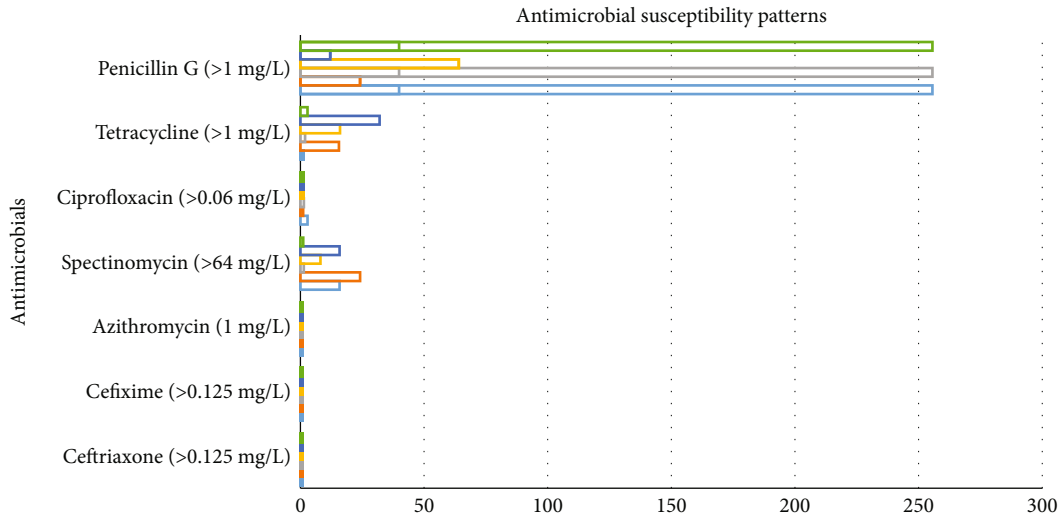
Table 1: Characteristics of the antenatal women enrolled in this study. The infection status of *N. gonorrhoeae* is based on the data from culture.

Status	Negative ($N = 301$)	Positive ($N = 6$)	p value	Overall ($N = 307$)
Age			0.102	
Mean ± SD (CV%)	29.4 ± 6.23 (21.2)	25.2 ± 3.19 (12.7)		29.3 ± 6.21 (21.2)
Median (Q1-Q3)	29.0 (24.0-34.0)	25.5 (22.8-27.5)	Rank sum test	29.0 (24.0-34.0)
Min–Max	19.0-45.0	21.0-29.0		19.0-45.0
Current abnormal vaginal discharge			1.000	
No	241 (80.1%)	5 (83.3%)		246 (80.1%)
Yes	60 (19.9%)	1 (16.7%)		61 (19.9%)
Married			1.000	
No	264 (87.7%)	6 (100%)		270 (87.9%)
Yes	37 (12.3%)	0 (0%)		37 (12.1%)
Regular sex partner			0.424	
No	104 (34.6%)	3 (50.0%)		107 (34.9%)
Yes	197 (65.4%)	3 (50.0%)		200 (65.1%)
Co habiting			0.407	
No	176 (58.5%)	5 (83.3%)		181 (59.0%)
Yes	125 (41.5%)	1 (16.7%)		126 (41.0%)
Lifetime sex partners			0.108	
>4	35 (11.6%)	0 (0%)		35 (11.4%)
1	80 (26.6%)	4 (66.7%)		84 (27.4%)
2 to 4	186 (61.8%)	2 (33.3%)		188 (61.2%)
Partner has other partners			0.601	
Do not know	169 (56.1%)	5 (83.3%)		174 (56.7%)
No	91 (30.2%)	1 (16.7%)		92 (30.0%)
Yes	41 (13.6%)	0 (0%)		41 (13.4%)
Condom use			0.638	
Always	23 (7.6%)	0 (0%)		23 (7.5%)
Never	53 (17.6%)	2 (33.3%)		55 (17.9%)
Rarely	6 (2.0%)	0 (0%)		6 (2.0%)
Sometimes	219 (72.8%)	4 (66.7%)		223 (72.6%)
Trimester			1.000	
1st	11 (3.7%)	0 (0%)		11 (3.6%)
2nd	96 (31.9%)	2 (33.3%)		98 (31.9%)
3rd	194 (64.5%)	4 (66.7%)		198 (64.5%)
Treated for STIs in the past			0.669	
No	205 (68.1%)	5 (83.3%)		210 (68.4%)
Yes	96 (31.9%)	1 (16.7%)		97 (31.6%)

(87.9%), reported "sometimes" using condoms (72.6%), and were not treated for STIs in the past (68.4%) (Table 1).

The p values are based on nonmissing cases only (tableStack).

3.2. Antimicrobial Susceptibility Testing. All 6 isolates produced antimicrobial susceptibility results (Figure 1). WHO reference strains with known MIC values were included as controls. The WHO strains produced the desired results thereby validating the Etest™ MIC results obtained. High MIC values to penicillin G (12-64 mg/L) indicating a resistant phenotype were observed for all isolates tested, with 50% of the isolates displaying complete resistance. Of the 6 isolates, 1 isolate exhibited an intermediate phenotype for tetracycline (1 mg/L) whereas the remaining 5 isolates showed resistance (1.9-32 mg/L). Five of the 6 isolates showed resistance to ciprofloxacin (1.16-3 mg/L) with 1 isolate still displaying the susceptible phenotype (0.003 mg/L). All 6 isolates displayed either dual or triple resistance to penicillin G, tetracycline or ciprofloxacin. All isolates showed susceptibility to spectinomycin (>64 mg/L), azithromycin (1 mg/L), ceftriaxone (>0.125 mg/L), and cefixime



	Ceftriaxone (>0.125 mg/L)	Cefixime (>0.125 mg/L)	Azithromycin (1 mg/L)	Spectinomycin (>64 mg/L)	Ciprofloxacin (>0.06 mg/L)	Tetracycline (>1 mg/L)	Penicillin G (>1 mg/L)
G247	0.002	0.002	0.016	0.75	0.16	3	256
G206	0.006	0.016	0.094	16	0.003	32	12
G180	0.004	0.002	0.047	8	0.5	16	64
G176	0.002	0.002	0.125	1.5	1.5	1.9	256
G136	0.012	0.002	0.094	24	1	16	24
G51	0.002	0.002	0.016	16	3	1	256

Figure 1: Etest™ data of emerging antimicrobial susceptibility/resistance patterns in *N. gonorrhoeae*. Patterns of resistance and susceptibility were determined by the 2019 EUCAST breakpoints.

(>0.125 mg/L). Isolates with complete susceptibility to azithromycin, ceftriaxone, and cefixime were observed (Figure 1).

4. Discussion

This study reported a prevalence estimate of 1.9% for *N. gonorrhoeae* in South African pregnant women by culture. Previous studies conducted in countries within Africa have reported rates of 2.3% in nonpregnant women [12]. Prevalence rates ranging from 4.9% to 6.1% for *N. gonorrhoeae* have been reported in pregnant women [24, 25]. In a cohort of pregnant women from Australia, predictors of being infected with *N. gonorrhoeae* included young age, harmful alcohol use, unwanted pregnancy, low birth weight, perinatal death, and coinfection with other STIs during pregnancy [25]. Other studies have also shown significant associations with sociodemographic, behavioural, and clinical factors and *N. gonorrhoeae* infection [24, 26]. However, our study showed no statistical significance with sociodemographic, behavioural, and clinical factors in relation to *N. gonorrhoeae* infection.

Over the past few years, *N. gonorrhoeae* has acquired AMR to penicillins, tetracyclines, and fluoroquinolones [14, 19, 20]. In this study, high MIC values to penicillin G indicating a resistant phenotype were observed for all isolates tested, with half of the isolates displaying complete resistance. Similarly, high MIC values for tetracycline (32 mg/L) and ciprofloxacin (3 mg/L) were observed in this study. Our findings are similar to other *N. gonorrhoeae* AMR studies conducted in South Africa. A study conducted by [20] in men and women presenting with male urethritis syndrome (MUS) and vaginal discharge syndrome (VDS) harboured *N. gonorrhoeae* that was resistant to penicillin, tetracycline, and fluoroquinolones. A 10-year *N. gonorrhoeae* AMR surveillance study conducted in Johannesburg, South Africa, showed high level penicillin and tetracycline resistance in male and female populations [27]. A more recent study conducted in Johannesburg, South Africa, also revealed the presence of a high number of isolates displaying tetracycline penicillin and ciprofloxacin resistance [28].

Despite the many *N. gonorrhoeae* AMR studies conducted in South Africa, there is no published data on *N. gonorrhoeae* AMR in pregnant populations, thereby lending novelty to this study. The study by Rambaran et al. (2019) identified isolates with MICs of 32 mg/L and 16 mg/L to tetracycline in men and women with MUS and VDS; these MICs were considered as high level resistance. In our study, similar MIC values were obtained for the asymptomatic pregnant women. The high level of tetracycline observed could have been the result of selective pressure by doxycycline which had previously been used in the syndromic management for the treatment of chlamydia infections [29, 30]. However, since 2015, doxycycline has been replaced by

azithromycin for MUS and VDS in the syndromic management approach. Resistance to azithromycin has been observed in South African men who have sex with men [28]. In our study isolates, resistance to azithromycin was not observed. However, there is still a need to monitor susceptibility patterns of this antimicrobial since it is part of syndromic management for the treatment of Chlamydia.

In this study, we identified isolates with a >10-fold increase above the breakpoint for ciprofloxacin. One isolate displayed a MIC of 3 mg/L to ciprofloxacin. Previous studies conducted in KwaZulu-Natal, South Africa, have reported MIC values of 1 mg/L for ciprofloxacin [31]. The 10-year *N. gonorrhoeae* AMR surveillance study conducted in Johannesburg, South Africa, showed MICs of ≥1 mg/L for ciprofloxacin. It was observed that from 2008 to 2016, the prevalence of high-level resistance to ciprofloxacin rose exponentially from 25% to 69% [27]. Due to emerging antimicrobial resistance, ciprofloxacin was replaced with cefixime in the syndromic management [32]. However, during the year 2012, two cases of decreased susceptibility to cefixime with treatment failure were observed in men who have sex with men [33]. In addition, ceftriaxone and spectinomycin were recommended for the treatment of infection with *N. gonorrhoeae* in pregnancy or in those who fail to respond to treatment with ciprofloxacin [34]. The current study has not observed any resistance to spectinomycin, cefixime, and ceftriaxone. However, more *N. gonorrhoeae* AMR studies need to be conducted on pregnant women since this data is severely lacking both nationally and internationally.

5. Conclusion

In this study, high MIC values to penicillin G, tetracycline, and ciprofloxacin were observed. Currently, there are no recent published studies from South Africa that have described *N. gonorrhoeae* AMR profiles in pregnant women. This study thereby fills this missing data. However, this study was limited in terms of the number of culture isolates. Despite this limitation, we were still able to identify resistant phenotypes. This study now provides evidence for the development of larger *N. gonorrhoeae* AMR surveillance studies in pregnant women. Despite the lack of ceftriaxone- and azithromycin-resistant isolates in the study population, it is still imperative to monitor patterns of emerging resistance since overtreatment in syndromic management can contribute to future resistance.

Data Availability

The data will be made available by the corresponding on request.

Conflicts of Interest

The authors declare no potential conflicts of interests with respect to the research, authorship, and/or publication of this article.

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