

Multiple drug allergy syndrome in pregnancy: Lessons for sexual health physicians

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Abstract

Co-existence of multiple drug allergies and pregnancy often results in vexing dilemmas for physicians. A 21-year-old pregnant woman presented with asymptomatic cervicitis with dual infection with *Chlamydia trachomatis* and *Neisseria gonorrhoeae* during her third trimester. She reported a history of generalised rash with mucous membrane involvement following use of both macrolides and penicillins. Her gonococcal infection was successfully treated with a single dose of intramuscular gentamicin and chlamydial infection with oral clindamycin and rifampicin.

Keywords

Chlamydia (*Chlamydia trachomatis*), bacterial disease, gonorrhoea (*Neisseria gonorrhoeae*), antibiotic, other

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Introduction

Multiple drug allergy syndrome (MDAS) describes patients with hypersensitivity reactions to two or more drug classes.¹ MDAS in pregnancy presents difficult decisions as some drug options may not be recommended or may be contraindicated. We report a case of dual infection with *N. gonorrhoeae* and *C. trachomatis* during the third trimester in a patient with MDAS. We describe an unusual but successful treatment regimen and explore options that are available to clinicians in these circumstances.

Case history

A 21-year-old woman contacted us as an asymptomatic contact of *N. gonorrhoeae*. Her regular partner had been treated at another service. Her last sexual contact with him was one week earlier. She was primigravid of 32 weeks with no obstetric complications. Her past medical history reported allergy to penicillin and erythromycin, with generalised, erythematous rashes and angioedema.

The national UK guidelines for gonorrhoea would recommend giving treatment to those in contact within the specified look-back period.² Given her asymptomatic presentation and allergic history, we first tested her for gonorrhoea and chlamydia with nucleic acid amplification tests (NAATs) – specifically, using the BD ProbeTec assay that uses the strand displacement amplification (SDA)

technique – and gonococcal (GC) culture after the incubation period of two weeks. We then planned to treat her with the appropriate antibiotics if her tests confirmed she was infected. The specimens for testing were obtained by self-taken vulvovaginal swabs.

Her NAATs were positive for both infections; her GC culture was negative, but this was not unexpected. We use AMIES transport medium and modified Thayer-Martin agar, but depending on duration of transport, isolation rates are sub-optimal compared to direct inoculation.³ Further, due to the COVID-19 pandemic, the sample for GC culture was self-taken instead of a physician-taken endocervical swab, increasing the possibility of a false negative.

The UK guideline for gonorrhoea (2018) recommends ceftriaxone (a third-generation cephalosporin) 1G intramuscular

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(IM), single dose (SD), spectinomycin 2G IM, SD, or azithromycin 2G oral, SD, during pregnancy. Although gentamicin 240 mg IM is an alternative treatment, it is not mentioned in the guideline for use in pregnancy, given the potential vestibulocochlear damage to the newborn.² Spectinomycin is not currently available in the United Kingdom so was not an option.

The guideline for chlamydia (2015) recommends treating during pregnancy with either azithromycin (1g 1 day, 500 mg for 2 days) or erythromycin. Amoxicillin (500 mg three times daily, for 7 days) is mentioned as an alternative. Although doxycycline is the first line treatment in most cases, it is contraindicated in pregnancy.⁴

We discussed the case with the multi-disciplinary team, including a consultant colleague in infectious diseases. Considering the risks due to the pregnancy, our patient was given gentamicin 240 mg IM, SD, to treat her gonorrhoea. Chlamydia was treated with rifampicin 600 mg (oral/once daily) and clindamycin 600 mg (oral/four times daily) for 7 days.

Two weeks after treatment, we did test of cure with dual NAATs, and the patient was cleared of both infections.

Discussion

Treatment during pregnancy is essential because both gonorrhoea and chlamydia in the mother can result in ophthalmia neonatorum in the newborn which can lead to corneal opacification. Corneal blindness is the third commonest cause of childhood blindness worldwide, following non-corneal causes such as congenital cataract and glaucoma.⁵

Considering the treatment decision for gonorrhoea, there is evidence of a penicillin allergy being predictive of first-generation cephalosporin allergy, but negligible cross allergy with second generation cephalosporins.⁶ Retrospectively, 5–10% of those reporting penicillin allergies showed an allergic reaction to cephalosporin, but these studies were found to have methodological flaws.⁷ More recent studies report that <1% of patients reporting penicillin allergy without skin testing experience cephalosporin allergy, approaching 2% in those with positive penicillin skin test.⁷

The R1 side chains of penicillins and cephalosporins determine the likelihood of cross sensitivity. Lower cross reactivity is observed with the newer cephalosporin antibiotics which have markedly different R1 chains compared to penicillins.^{7,8} Cephalosporins are usually avoided in patients with type I hypersensitivity to penicillin, but most clinicians consider the risk of cross reaction in people with only mild penicillin allergies to be acceptable. Further, chemical comparison of the specific penicillin that caused the allergy with the cephalosporin to be given should be done.^{9,10}

Therefore, we decided to avoid ceftriaxone to treat her gonococcal infection due to the patient's allergic reactions.

Vestibulocochlear nerve damage is a known risk for the neonate when aminoglycosides are used during the second

and third trimesters of pregnancy. The risk is considered small with gentamicin and tobramycin, but avoidance unless essential is the maxim, according to the British National Formulary (BNF) guidelines. A weight-based dose of gentamicin in pregnancy is recommended – if there is no suitable alternative – by the BNF and National Institute for Health and Care Excellence (NICE) guidelines. The recommended dose (240 mg IM SD) of gentamicin for gonococcal infection from the national guideline was below the recommended safe dose (260 mg for <50 kg patient and increasing with greater weight) during pregnancy for any condition in the BNF/NICE guidelines. Therefore, we treated our patient with gentamicin 240 mg IM SD. However, gentamicin is not as effective compared to ceftriaxone for gonococcal infection, with further research into alternatives to ceftriaxone being needed.¹¹

Considering the treatment decision for chlamydia, macrolides are infrequently reported to cause various types of allergic reaction, although data are scarce. Macrolides share similar chemical structures, and limited reports have demonstrated cross reactivity. Cross reactivity between 14 membered macrolides (clarithromycin and erythromycin) has been reported in single case studies, but the mechanism is unknown.¹² Cross reactivity between the 15 membered macrolide, azithromycin and erythromycin has been reported, and this is thought to be due to structural similarities.¹² Therefore, if a patient has a severe hypersensitivity reaction to a macrolide, then caution must be exercised before using another macrolide. It may be better to switch to an alternative class of medication. If a macrolide must be used in a patient with confirmed history of severe allergic reaction, then an allergy test and desensitisation should be conducted.¹² As our patient reported that she had a generalised, itchy rash with mucous membrane involvement, we decided to avoid azithromycin to treat her chlamydial infection.

There are no relevant controlled studies of doxycycline use in pregnant women to show safety. An expert review on doxycycline use during pregnancy concluded that a teratogenic risk is unlikely at therapeutic doses, but there are insufficient data to declare no risk.¹³ The risk of cosmetic staining of primary teeth by doxycycline is undetermined.

Historically, clindamycin was used to treat chlamydial infection, as well as being used instead of erythromycin for chlamydia cervicitis in pregnancy. In patients randomised to clindamycin 450 mg QID in one study, short-term eradication of chlamydia was better compared to erythromycin (93% vs 84%) with clindamycin being tolerated better.¹⁴ The BNF cautions use of clindamycin in the first trimester and states harm is not known for second and third trimesters.

Rifampicin was another historical option to treat chlamydial urethritis. In a double-blind therapeutic trial conducted among patients with non-gonococcal urethritis at Central Middlesex Hospital, England, UK, in the pre-NAAT era, rifampicin was given 600 mg once daily for 6 days

alongside minocycline. 123 patients with non-gonococcal urethritis received rifampicin, 53 of whom were chlamydia positive; *Chlamydia trachomatis* was only isolated from 1 out of 53 following treatment.¹⁵ The BNF states the risk of neonatal bleeding may be increased in the third trimester with rifampicin.

The national guidelines recommend tests of cure (with NAATs, also via SDA) 2 weeks after treatment for gonorrhoea and 5 weeks after treatment for chlamydia. However, we did both tests after 2 weeks for convenience and both infections had been cleared. Tests of cure are not routinely performed for chlamydia in non-pregnant patients, but a TOC is recommended for pregnant women with chlamydia.

The patient's partner was treated in another clinic, and we advised no unprotected sexual contact until the test of cure had returned negative from both of them.

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Author contributions

Dr Mohamed Buhary is the principal author of this case report and managed the patient. Dr McGregor was the infectious diseases consultant we consulted for his expert opinion. Dr McSorley was the clinical supervisor and provided advice. Dr Friday was the lead consultant and provided advice.

Declaration of conflicting interests

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Ethical approval/Patient consent

The consent of the patient was taken before writing the report. Her consent was recorded in her medical history, and she will receive a copy of the case history following acceptance for publication.

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