Recurrent urethral pain syndrome in a pregnant patient: a case for low-dose broad spectrum oral antibiotics

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Abstract
Introduction
As obstetricians, gynaecologists and urologists, we routinely see patients who complain of symptoms of urinary tract infections but have repeated clean catch urine specimen remaining sterile, yet they respond positively to a short course of antibiotics. Sometimes, the response is sustained, on other occasions, the response is short-lived, but the response is usually satisfying to the patient. Surely, this cannot simply be the result of the known placebo effect. This paper makes a case for low-dose broad spectrum oral antibiotics in a pregnant patient with recurrent urethral pain syndrome.

Case report
We performed an extensive English language electronic search in the following databases: Medline, Embase, Amed, Cinahl, Pubmed, Cochrane library and Trip; and did some search using the following search terms: urethral syndrome, urethral diseases in pregnancy, urologic diseases aetiology, presentation, treatment, outcome and therapeutics from 1951 to 2012. We found a paper by Baerheim and colleagues, who observed that there is equal symptomatic outcome after antibiotic treatment of acute lower urinary tract infection and the acute urethral syndrome in adult women. Their work did not include pregnant patients.

Emboldened by the strength of the findings by Baerheim et al. and our observations in a case of a 24-year-old gravid female with recurrent episodes of urethral syndrome, which subsided when she was placed on low-dose oral co-amoxiclav, but rebounding leading to urinary retention when the antibiotic was discontinued; we make a case for low-dose oral antibiotics in a pregnant patient with recurrent urethral syndrome.

Conclusion
Since this is only a case report, it restricts us from making generalised statements, we would suggest that consideration be given to the use of broad-based antibiotics excreted by the kidneys in pregnant patients presenting with the urethral pain syndrome.

Introduction
The literature is replete with arguments and counterarguments about the role of microbes in the aetiology of the urethral syndrome1-5. Some contend that the urethral syndrome is a manifestation of urinary tract infection by fastidious organisms. Others claim that it is the result of anatomic defect in the urethra, such as vesicourethral stenosis.6,7 Still others claim that it is the result of relative oestrogen deficiency.8 The view that the urethral syndrome is the result of urinary tract infection with fastidious organisms has led to a review of Kass’s criterion for significant bacteruria9.

Baerheim and colleagues1 have noted that there is equal symptomatic outcome after antibacterial treatment of acute lower urinary tract infection and the acute urethral syndrome in adult women. Maccoll9 suggests that the urethral syndrome is caused by infections with ‘fastidious bacteria’. These organisms, chiefly lactobacilli (but including streptococci and diphtheroids), live as commensals in the lower genital tract. The arguments implicating fastidious bacteria has proven controversial because Gillespie et al.10 were able to isolate no greater numbers of fastidious bacteria from the urine of patients with the urethral syndrome than from the urine of asymptomatic women. Additionally, Cooper et al.11 reported that treatment of the urethral syndrome with co-amoxiclav active against lactobacilli gave the same ‘cure rate’ as treatment with fosfomycin, which is inactive against lactobacilli.

The varying success, resulting from attempted treatment of patients diagnosed with the urethral pain syndrome with antibiotics, has led others to question whether the urethral pain syndrome is simply a low-grade urinary tract infection. We make a case for the continued use of low-dose prophylactic antibiotic treatment in pregnant women with recurrent urethral syndrome.

Case report
A 24-year-old primiparous Caucasian female, at 24 weeks of pregnancy, presented to the outpatient department of a district general hospital complaining of frequency, hesitancy and tail end burning sensation on voiding but no history of urinary retention, poor urinary stream or other symptoms of voiding dysfunction. Midstream urine was clear and the patient was encouraged to increase her water intake. Her symptoms persisted and she was reviewed by her general practitioner 4 days later, who repeated her midstream urine...
specimen. Though this specimen was clear; she was started on an empirical course of co-amoxiclav for a week. She took 375 mg three times a day for a week and, interestingly, her symptoms subsided; but, on completion of the week’s course, the symptoms immediately recurred.

She was referred to the day assessment unit at 25 weeks and 4 days, where she had a detailed history and a physical examination performed. The only significant finding in this patient was tenderness on the anterior vaginal wall along the distal two-thirds to half of the urethra, in the region of the paraurethral glands. Her MSU on the two previous occasions were sterile, there was no growth on culture and the microscopy was negative for red blood cells, there were only 10 white blood cells per microlitre and the bacterial count was less than 50 per microlitre. She suffered from seborrhoeic dermatitis and, in her family history, she indicated that her elder sister had similar problems in her pregnancy. She was diagnosed with the urethral pain syndrome. There was no voiding dysfunction as her bladder diary revealed urinary frequency of six times per day and her voided volumes ranged between 350 mL and 420 mL per void.

The patient’s symptoms, collagen vascular disease and family history increased the probability that she may also be suffering from the urethral pain syndrome. Her reported symptomatic improvement on oral antibiotics in the presence of sterile midstream urine cultures was interesting. It was decided that she should be kept on a low dose (375 mg once per day) of co-amoxiclav for the duration of her pregnancy. This was commenced with good effect from 26 weeks gestation.

At 28 weeks gestation, she was seen by her urologist, who disagreed with the management plan and proceeded to discontinue the antibiotics. The patient’s symptoms immediately returned and she promptly went into urinary retention. She was catheterised and the catheter was left in situ overnight while her antibiotic regime was recommenced, initially, three times a day for 5 days then 375 mg daily. She passed the trial without catheter the following morning and she was kept on low-dose oral co-amoxiclav for the remainder of her pregnancy with good effect. All her midstream urine cultures were sterile for both regular microbes and fastidious organisms.

Discussion
Antibiotics are either bactericidal or bacteriostatic. Co-amoxiclav lacks antispasmodic activity, yet in the above case it seems, at least superficially, to be acting as an antispasmodic agent. How was that possible? This, we believe, was the result of an indirect effect of the action of the metabolites of co-amoxiclav on the microbes.

The literature is replete with various arguments implicating the role of microbes in the urethral pain syndrome. Some have inferred that urethral pain syndrome is a low grade urinary tract infection with fastidious organisms. The evidence for this assumption is weak and has been rejected by others who used antibiotics to treat the urethral pain syndrome with varying results. Cooper et al. showed that fosomycin, an antibiotic, which is inactive against lactobacilli gave the same ‘cure rates’ as co-amoxiclav, which is active against lactobacilli.

Gittes postulates that the syndrome is caused by female prostatitis, and that it is occasionally referred to as female prostatitis.

The success, in our patient, with the use of co-amoxiclav was at best fortuitous based on: (a) the knowledge that co-amoxiclav is safe in pregnancy despite its recent association with necrotising enterolitis in preterm babies, (b) the excretion of co-amoxiclav and its metabolites by the kidneys, leading to high concentrations of its metabolites with both bacteriostatic and bactericidal properties in the urine and (c) the patient not being allergic to co-amoxiclav.

The potassium sensitivity test informs us that in patients with the urethral pain syndrome, over 50% of them have a positive test result. The mucosal barrier in patients showing positive test results is defective and hence allows potassium to diffuse from the urethral lumen across the mucosa into the sub-mucosal space, where, because of its high concentration in the urine (40–140 meq), it is toxic to both the muscles and nerves leading to the tail end and post-void discomfort these patients experience at the time of micturition. The urethra responds to this discomfort by going into spasms as evidenced by the increased tone at the level of the external urethral sphincter seen on urethral pressure profilometry in these patients. This leads to the creation of eddy currents and further damage to the mucosa and sub-mucosa. The proximity of the urethra to the outside and to the vagina in the female allows for easy access to microbes which, though may be commensals, in the presence of this trauma and in the absence of dead tissue, find an ideal environment in which they can proliferate, leading to further localised tissue injury and discomfort.

The antibiotics-co-amoxiclav, as used in this case-functioned in keeping the microbial activity to a minimum by inducing bacteriostasis. Thus, when the drug was removed, the microbes resumed their activity, leading to an almost instantaneous return of the patient’s symptoms as was seen in the case report above.

We know that the urinary retention was the result of urethral spasm because Raz and Smith were able to show spasticity of the external urethral sphincter on urethral pressure profilometry in women with the urethral pain syndrome. Lipsky, in a small case series, reported incomplete relaxation or spasm of the external striated sphincter. Barbalias and Meares found a high maximum

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**FOR CITATION PURPOSES:** Phillip H, Okewole A. Recurrent urethral pain syndrome in a pregnant patient: a case for low-dose broad spectrum oral antibiotics. OA Case Reports 2013 Sep 10;2(10):93.
urethral closure pressure in patients suffering from the urethral pain syndrome. This leads to low flow rates and many of these patients present with urinary retention or have experienced urinary retention at some time in the course of the disease. Treatment of these patients medically, with α-blockers or muscle relaxants such as diazepam or amitriptyline, has been reported to be equally or more effective than the more invasive surgical option.

Conclusion

This case report gives a useful insight into the role of microorganisms in the persistence and recurrence of the symptoms associated with the urethral pain syndrome.

Co-amoxiclav, as used in this case, was a fortuitous choice mainly because it is a broad spectrum antibiotic and it is excreted by the kidneys allowing for the presence of various metabolites in the urine, which has both bactericidal and bacteriostatic properties. Unfortunately, in the above case, it would seem that the bacteriostatic properties were the ones predominantly at work, since the symptoms recurred on cessation of the drug. The lesions were not healed because the microbes were still present and were only dormant.

Since this is only a case report that restricts us from making generalised statements, we would suggest that consideration be given to the use of broad-based antibiotics excreted by the kidneys in pregnant patients presenting with the urethral pain syndrome. As demonstrated above, a low-dose preparation of this antibiotic can be used throughout pregnancy with no ill effects on the foetus. This case report and the work of Baerheim, who observed that there is equal symptomatic outcome after antibacterial treatment of acute lower urinary tract infection and the acute urethral pain syndrome. As demonstrated above, a low-dose preparation of this antibiotic can be used throughout pregnancy with no ill effects on the foetus. This case report and the work of Baerheim, who observed that there is equal symptomatic outcome after antibacterial treatment of acute lower urinary tract infection and the acute urethral pain syndrome.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

References


Case report

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Case report
