

Which antibiotics are appropriate for treating bacteriuria in pregnancy?

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Bacteriuria in pregnancy, with or without clinical symptoms, is frequent. If left untreated, it can in 20–30% of cases lead to acute pyelonephritis, which is a serious threat to the mother and fetus, increasing the risk of preterm labour and low birthweight infants. This paper is a review of the literature concerning antibacterial treatment of bacteriuria in pregnancy. It is crucial to ensure that drugs to be used in pregnancy are safe and effective. Established first-line drugs such as ampicillin (pivampicillin) and amoxicillin, and other commonly used treatments such as trimethoprim–sulphamethoxazole, are associated with a high degree of resistance in *Escherichia coli*, the most common pathogen in the urinary tract. A recent survey of physicians in Denmark, Finland, Norway and Sweden confirms that β -lactam antibiotics (particularly pivmecillinam) and nitrofurantoin are the drugs of first choice in the treatment of bacteriuria in pregnancy in the Nordic countries. No teratogenic effects have been associated with these agents. In contrast to nitrofurantoin, pivmecillinam is also efficient against pyelonephritis. In spite of resistance in *E. coli* and possible adverse effects on the fetus, many physicians still prescribe sulphonamides during the first two trimesters of pregnancy.

Introduction

Bacteriuria, either asymptomatic or symptomatic, is common in pregnancy.^{1–3} If left untreated, asymptomatic bacteriuria will lead to acute pyelonephritis in 20–30% of cases. This may result in low birthweight infants, premature delivery and, occasionally, stillbirth,⁴ so it is a serious threat for the mother and the unborn child.⁵ Bacteriuria is associated with a 50% increase in the risk of low birthweight and a significant increase in the risk of premature delivery,⁶ pre-eclampsia,⁷ hypertension, anaemia⁸ and post-partum endometritis.⁹ It is well documented that effective treatment of asymptomatic bacteriuria significantly reduces the incidence of pyelonephritis, premature deliveries and low birthweight infants.^{4,9}

When selecting drugs to use in pregnancy, well-established agents with well-known properties are generally preferred to newer ones. For obvious ethical reasons, research on the effects of drugs on the fetus is mainly restricted to retrospective studies and case reports. In the past two decades, several new antibacterial agents have been developed in response to the worldwide problem of increasing bacterial resistance. Before these agents are widely used in pregnancy, it is essential to ensure that they are safe for both the pregnant woman and the fetus.

A Medline search was used to find publications in English or a Scandinavian language concerning the antibacterial treatment of bacteriuria in pregnancy. The efficacy of the major drugs used to treat bacteriuria in pregnancy is reviewed here, as are their effects on the mother and fetus. The results are discussed in light of current prescription practice for bacteriuria in pregnancy.

The particular problems of pregnancy

Asymptomatic bacteriuria in women who are not pregnant often does not have a significant effect and may not persist.¹⁰ During pregnancy, bacterial growth is favoured by the increased urinary content of amino acids, vitamins and other nutrients, which encourage the persistence of infection.¹¹ Slowing of urine flow secondary to the dilation of the urinary tract, which may be caused by hormonal and mechanical factors, can add to this effect.¹² In addition, some maternal defence mechanisms are less effective during pregnancy.¹³

Asymptomatic bacteriuria is usually reported to occur in 2–7% of all pregnancies, depending on the population studied.^{1–3} *Escherichia coli* is the most frequent pathogen,

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being reported in *c.*70–95% of cases.^{13–15} Other Enterobacteriaceae and group B streptococci cause bacteriuria in pregnancy and several reports about 20 years ago (see Brumfitt *et al.*,¹⁴ for example) showed that Micrococcaceae (particularly *Staphylococcus saprophyticus*) were significant urinary tract pathogens in non-pregnant women.

Pregnancy is associated with a physiological increase ($\leq 50\%$) in the glomerular filtration rate, which increases the elimination rate of drugs excreted via the kidneys.¹³ This, together with frequent polyuria in pregnancy,¹³ reduces the time for which a drug is present in urine and makes it necessary to increase the dose of some hydrophilic drugs to ensure efficacy.¹⁶

Organogenesis, which occurs during the first trimester of pregnancy, is the stage at which the fetus is most vulnerable to teratogenesis. Environmental factors that are recognized to have teratogenic effects in pregnancy are irradiation, deficiency^{17,18} or overdosage¹⁹ of some vitamins and certain drugs.²⁰

Antibacterial agents for use in bacteriuria in pregnancy

β -Lactam antibiotics

β -Lactam antibiotics, including penicillins (such as ampicillin, amoxycillin and mecillinam) and cephalosporins (such as cephalexin) are some of the oldest antibiotics used to treat bacterial infections. Many studies have shown that the pharmacokinetics of some β -lactam antibiotics are altered during pregnancy, with faster renal elimination and lower plasma concentrations of these drugs. Therefore, for many of these agents, the dose should be increased in pregnancy.¹⁶ *β -Lactam antibiotics* are generally well tolerated and, although they produce a wide variety of side-effects, these are generally mild and self-limiting. No β -lactam antibiotic is known to be teratogenic.²¹

Penicillins. Penicillin G is the recommended antibiotic for treating infections caused by group B streptococci. Ampicillin is poorly absorbed by the oral route and therefore may require parenteral administration. However, the greatest limitation to its use in urinary tract infection (UTI) is the increasing level of resistance in *E. coli*. The plasma concentrations of ampicillin in pregnancy may be $\leq 50\%$ lower than in non-pregnant women.²² Therefore, the dose or the frequency of administration should be increased in pregnancy, particularly after the second trimester. The drug reduces the serum and urinary concentrations of oestriol and is, therefore, less suitable in late stages of pregnancy.^{23,24}

Ampicillin esters with improved absorption, such as pivampicillin, are suitable for oral administration. However, pivampicillin should not be given to patients with inborn errors of carnitine metabolism, because the ester

component is excreted conjugated to carnitine and may result in symptomatic carnitine deficiency in these patients.

Amoxycillin is another oral alternative to ampicillin, but exhibits complete cross-resistance with ampicillin. Amoxycillin may be used in normal dosage in pregnancy but, as with ampicillin, the high level of resistant *E. coli* limits its use.

Mecillinam is a penicillin that acts selectively against Gram-negative bacilli. Oral therapy is given as the ester, pivmecillinam.²⁵ Although pivmecillinam is renally excreted, increasing the dose in pregnancy is not necessary.²⁶ A major advantage of pivmecillinam is that there is little resistance in *E. coli*. A number of reports have confirmed the efficacy of pivmecillinam in bacteriuria in pregnancy.^{14,27,28} At the currently recommended dosage, pivmecillinam is well tolerated.^{27,28} Like pivampicillin, pivmecillinam should not be given to patients with inborn errors of carnitine metabolism. No teratogenic effects of pivmecillinam have been reported even after 3 months' use.²⁸ Mecillinam can be given intravenously in acute pyelonephritis.

Co-amoxiclav, which is effective in treating infections caused by ampicillin-resistant bacteria, has been used to treat bacteriuria in pregnancy, but experience concerning its safety is limited.²⁹

Cephalosporins. Cephalosporins may be used to treat acute pyelonephritis in pregnancy² and are alternatives if there is bacterial resistance to the first-line drugs.³⁰ Most regimens involve oral treatment for 7 or 10 days. Cephalexin is probably the oral cephalosporin that has been most widely used in pregnancy.¹³

Cephadrine is of established value and of similar efficacy to pivmecillinam,¹⁴ although side-effects (particularly vaginal irritation) appear to be more common in patients treated with cephadrine than in those receiving pivmecillinam. Cephadoxil has been used in Finland for acute UTI in pregnancy.³¹ As with the penicillins, oral cephalosporins are considered safe in pregnancy.^{14,21}

Cefazolin and the third-generation cephalosporin, ceftriaxone, are effective in the treatment of acute pyelonephritis.³² However, if ceftriaxone is given shortly before birth, there is a risk of kernicterus because of its high degree of protein binding. Further experience is required before its potential role, and that of other third-generation cephalosporins, can be fully established.

Lincosamides. Clindamycin is appropriate treatment for penicillin-allergic women with infection caused by group B streptococci.³³ There are no reports of teratogenicity. Increasing the dose in pregnancy is not necessary.

Aminoglycosides. Aminoglycosides attain high renal tissue concentrations and are effective in acute pyelonephritis.³⁰ They cross the placenta and could, theoretically, be ototoxic and perhaps nephrotoxic to the fetus. Fetal toxicity has

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followed streptomycin use in pregnancy. If aminoglycosides are used to treat pyelonephritis in pregnancy, the maternal serum concentration should be carefully monitored and the dose adjusted to avoid toxicity.

Sulphonamides. Sulphonamides are not recommended as first-line drugs in pregnancy because of the increasing problem of *E. coli* resistance and because of their side-effects. They may inhibit folate metabolism and allergic reactions are relatively frequent. Sulphonamides should not be used in the last trimester because of the well-known risk of kernicterus in the newborn,³⁴ although this is probably lower than once thought.

Trimethoprim. In some countries, such as the UK, where trimethoprim has been used widely to treat UTIs, there has been a marked increase in the level of trimethoprim-resistant *E. coli*.³⁵ The incidence of minor side-effects with trimethoprim is similar to that with other agents, but side-effects seem to occur most frequently when trimethoprim is given as a fixed dose in combination with a sulphonamide. Trimethoprim and trimethoprim-containing preparations should not be used in the first trimester of pregnancy because trimethoprim inhibits folate metabolism.^{2,21,36} Even a moderate decrease in the concentration of folate in red blood cells is associated with an increased risk of neural tube defects in genetically disposed individuals.³⁷

Quinolones. Fluoroquinolones attain high renal tissue concentrations and have been used as alternatives in acute pyelonephritis in the presence of resistance to first-line treatments.³⁰ Although there is a low degree of resistance to quinolones in *E. coli*, there is concern that this will increase if quinolones are used more widely.³⁸ On ecological grounds, the use of quinolones in uncomplicated UTIs is not recommended. Central nervous system toxicity has been reported with the quinolones.³⁹ Quinolones may cause haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase deficiency and arthropathy has been associated with quinolone use in young animals. Their use during pregnancy is, therefore, not recommended.²

Nitrofurantoin. Nitrofurantoin concentrations achieve therapeutic levels only in urine, so this agent can only be used to treat infections of the lower urinary tract. Although active against *E. coli*, nitrofurantoin is not active against *Proteus* spp. The main side-effects of nitrofurantoin are anorexia, nausea and vomiting, which are less common with macrocrystalline formulations.²¹ Serious adverse effects are very rare, but can involve the liver, lungs and the nervous system.³⁰ Further, nitrofurantoin may cause haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase deficiency. Although nitrofurantoin has shown mutagenicity *in vitro*, a meta-analysis concluded that there was no significant correlation between nitro-

furantoin treatment and fetal malformations.⁴⁰ Nitrofurantoin is considered a suitable agent for treating bacteriuria in pregnancy.²¹

Fosfomycin trometamol. Fosfomycin, a derivative of phosphonic acid, can be used to treat uncomplicated infections of the lower urinary tract, either intravenously, or orally with its trometamol salt. Comparative clinical trials suggest that a single dose of fosfomycin is as effective clinically as a 7–10 day treatment regimen of nitrofurantoin, norfloxacin or co-trimoxazole.⁴¹ The drug is well tolerated, with a very low incidence of adverse effects.^{41,42} No teratogenic effects have been associated with the use of fosfomycin trometamol in clinical studies or in animals,⁴¹ but there is only limited experience of this drug in pregnancy so caution is advocated until its real value can be assessed.

Discussion

Establishing the diagnosis of bacteriuria in pregnancy

The physiological changes of pregnancy may make it more difficult to diagnose bacteriuria. Increased physiological vaginal discharge, increased laxity of the pelvic tissues, and enlarging abdominal mass all increase the possibility of vulvovaginal contamination of a midstream urine (MSU) specimen. Even with satisfactory standard techniques, the false positive rate may exceed 40%.⁴³ For the diagnosis of bacteriuria based on MSU specimens, a count of $>10^5$ cfu/mL is required on two different occasions. Some authors suggest a lower concentration of bacteria for the diagnosis, in particular for bacteriuria with *E. coli*.³⁰ The diagnosis can be confirmed by suprapubic aspiration, which is safe in pregnancy up to 32 weeks. During the later stages of pregnancy and in patients unable to fill their bladder sufficiently, catheter specimens of urine are almost as accurate.

Current trends in the prescription of antibiotics to treat bacteriuria in pregnancy

The practice of prescription of antibacterial drugs in pregnancy varies in different countries. In the USA, amoxicillin use is very common,¹⁰ whereas in Canada the recommended first-line treatment includes trimethoprim and nitrofurantoin. Penicillins and cephalosporins are advocated in the UK.⁴⁴ Pivmecillinam is the most frequently prescribed antibiotic for UTIs in both Sweden and Finland.^{16,31} The Norwegian reference group for urinary tract diseases (NSAMs referansgruppe for urinveissykdommer) has recommended 3 days' treatment with amoxicillin, pivampicillin, pivmecillinam or a cephalosporin in asymptomatic bacteriuria in pregnancy.⁴⁵ Recently, the prescribing practice of 560 general practitioners and obstetricians in Denmark, Finland, Norway and Sweden was surveyed

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Table. Prescribing practice of 560 general practitioners and obstetricians for UTI in pregnancy in Nordic countries in 1 year

| Drug | First trimester | | Second trimester | | Third trimester | |
|-----------------|-----------------|------|------------------|------|-----------------|------|
| | <i>n</i> | % | <i>n</i> | % | <i>n</i> | % |
| Amoxicillin | 119/560 | 21.3 | 109/560 | 19.5 | 118/560 | 21.1 |
| Nitrofurantoin | 151/560 | 27.0 | 150/560 | 26.8 | 143/560 | 25.5 |
| Pivampicillin | 60/560 | 10.7 | 69/560 | 12.3 | 90/560 | 16.1 |
| Pivmecillinam | 266/560 | 47.5 | 251/560 | 44.8 | 266/560 | 47.5 |
| Sulphamethizole | 163/560 | 29.1 | 135/560 | 24.1 | 41/560 | 7.3 |

The Table shows the number of general practitioners and obstetricians in Denmark, Finland, Norway and Sweden who reported that they had prescribed amoxicillin, nitrofurantoin, pivampicillin, pivmecillinam or sulphamethizole to treat UTI in pregnancy in the previous year (1999); 560 physicians returned the questionnaire. These five antibiotics were reported to be the most frequently prescribed for UTI in pregnancy (Tvede, M., personal communication).

(Tvede, M., personal communication). Pivmecillinam was the most commonly used antibiotic for UTI in pregnancy in these countries (Table).

There is a universal trend towards giving shorter treatment courses. This is expected to improve patient compliance and tolerance, particularly in reducing the occurrence of vaginal candidosis. Some authors have been concerned that shorter treatment courses may not be sufficient in pregnancy, but recent research confirms that even a single-dose regimen may be as efficient in pregnant as in non-pregnant patients.

Which antibiotics are appropriate for treating bacteriuria in pregnancy?

Apart from economic arguments, the problem of selecting an antibacterial agent for treatment in pregnancy is the possible conflict between a well-established drug that is well tolerated and empirically known to be harmless to the mother and the fetus, and a drug to which there is a low level of bacterial resistance.

The most frequent side-effects with oral antimicrobial drugs are related to the gastrointestinal tract, the female genital tract and the skin.²¹ Allergic reactions may occur, in particular with the sulphonamides and penicillins (including penicillin esters). No β -lactam antibiotic is known to have a teratogenic effect. Similarly, there is a general acceptance that the use of nitrofurantoin in pregnancy is acceptable. The folate inhibitors trimethoprim and sulphonamides are not universally regarded as safe in pregnancy and are best avoided. The safety of aminoglycosides has not been established although they are occasionally used in severe pyelonephritis in the last trimester. Fluoroquinolones are contraindicated because of the potential risk of arthropathy.

Ampicillin and the related compounds, pivampicillin

and amoxicillin, are all associated with a high level of resistance in the most common pathogen in the urinary tract, *E. coli*. There is a similar high level of resistance to sulphonamides, and to trimethoprim in some countries, such as the UK.³⁵ Resistance to cephalosporins, nitrofurantoin and mecillinam is low. There is also a low level of resistance to the fluoroquinolones although their widespread use is not recommended as it may encourage development of resistance.

Short courses of treatment require careful follow-up. Regardless of whether a conventional course or a shorter course is given, primary treatment failures and relapses and reinfections should be treated with a 7 day course of a different agent according to *in vitro* susceptibility. Patients with repeated episodes of bacteriuria should be considered for long-term low-dose prophylactic therapy. Nitrofurantoin or cephalexin is suitable.

In conclusion, certain β -lactam antibiotics and nitrofurantoin seem to fulfil the necessary safety and efficacy criteria to be used to treat bacteriuria in pregnancy. Pivmecillinam is also efficient against pyelonephritis and is currently the most frequently used antibiotic in UTI in pregnancy in Norway, Denmark, Sweden and Finland.

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