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Treatment of Sexually Transmitted Bacterial Diseases in Pregnant Women

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Abstract

Testing for and treating sexually transmitted diseases (STDs) in pregnant women deserves special attention. Treatment possibilities are limited because of potential risks for the developing fetus, and because effects can differ in pregnant compared with non-pregnant women, re-infection may be missed because of the intrinsic delicacy of contact-tracing during pregnancy and because pregnant women are more reluctant to take the prescribed medication in its full dose, if at all. However, the devastating effects of some of these genital infections far outweigh any potential adverse effects of treatment.

Although active syphilis has become a rarity in most Western countries, it is still prevalent in South America, Africa and South-East Asia. Benzathine benzylpenicillin (2.4 million units once or, safer, twice 7 days apart) is the treatment of choice, although patients with syphilis of longer standing require 3 weekly injections as well as extensive investigation into whether there has been any damage due to tertiary syphilis. Despite declining rates of gonorrhea, the relative rate of penicillinase-producing strains is increasing, especially in South-East Asia. The recommended treatment is intramuscular ceftriaxone (125 or 250mg) or oral cefixime 400mg. Despite good safety records after accidental use, fluoroquinolones are contraindicated during pregnancy. An alternative to a fluoroquinolone in pregnant women with combined gonorrhea and chlamydial infection is oral azithromycin 1 or 2g. Azithromycin as a single 1g dose is also preferable to a 7 day course of erythromycin 500mg 4 times a day for patients with chlamydial infection. Eradication of *Haemophilus ducreyi* in patients with chancroid can also be achieved with these regimens or intramuscular ceftriaxone 250mg. *Trichomonas vaginalis*, which is often seen as a co-infection, has been linked to an increased risk of preterm birth. Patients infected with this parasite

should therefore received metronidazole 500mg twice daily for 7 days as earlier fears of teratogenesis in humans have not been confirmed by recent data.

Bacterial vaginosis is also associated with preterm delivery in certain risk groups, such as women with a history of preterm birth or of low maternal weight. Such an association is yet to be convincingly proven in other women. The current advice is to treat only women diagnosed with bacterial vaginosis who also present other risk factors for preterm delivery. The treatment of choice is oral metronidazole 1 g/day for 5 days. The possible reduction of preterm birth by vaginally applied metronidazole or clindamycin is still under investigation.

In general, both test of cure and re-testing after several weeks are advisable in most pregnant patients with STDs, because partner notification and treatment are likely to be less efficient than outside pregnancy and the impact of inadequately treated or recurrent disease is greater because of the added risk to the fetus. Every diagnosis of an STD warrants a full screen for concomitant genital disease. Most ulcerative genital infections, as well as abnormal vaginal flora and bacterial vaginosis, increase the sexual transmission efficiency of HIV, necessitating even more stringent screening for and treating of STD during pregnancy.

Treatment of any disease in pregnancy poses specific problems. Many medications are contraindicated during pregnancy and possible fetal adverse effects of many other medications have not been adequately studied in large, randomised trials. Pregnant women in most Western countries are very reluctant to use any medication, even those considered to have no safety problems. Genital infections often remain unnoticed during pregnancy, as their signs and symptoms may be seen as part of the normal discomfort of pregnancy. Many drugs, such as erythromycin, are not well tolerated during pregnancy, so that patients do not adhere to the treatment protocol properly. During pregnancy, the link to other partners or the partners of their sexual partner is often either ignored or not even made, thus increasing the likelihood of re-infection after curative treatment.

Since a second patient, the fetus, may also be endangered, the case for screening and treating for asymptomatic genital infectious disease may be even stronger during pregnancy than at other times. The need for screening for sexually transmitted diseases (STDs) during pregnancy depends on the prevalence of the condition, its severity and the cost-benefit analysis for a population or risk group. However, once screening is instituted, adequate treatment must automatically follow the diagnosis. Test of cure is not generally advised, but may be considered in STDs during pregnancy, as the consequences for the fetus may be severe if treatment is inadequate. For a few genital infections with a severe impact on the outcome of the pregnancy, such as syphilis, gonorrhoea and trichomonasis, a 'screen and treat' policy is almost always cost-effective.[1] Partner notification and treatment, even if he does not want to be tested, is always warranted. Locating partners may be difficult: many women will not admit to extramarital sexual relations during pregnancy and will bring a non-infected partner, not infrequently their legal husband, in for treatment.[2]

1. Syphilis

Syphilis screening should be performed even if only 1 in 10 000 is expected to be positive.[3] According to the Centers for Disease Control and Prevention (CDC) guidelines, early syphilis (primary, secondary or latent stage, lasting less than 1 year) should be treated with only one intramuscular injection of 2.4 million units (MU) of benzathine benzylpenicillin (benzathine penicillin G).[4] The late form (lasting longer than 1 year) requires 3 of these injections one week apart. A recent study shows a 98% success rate in the prevention of congenital syphilis with a single intramuscular dose of benzathine benzylpenicillin 2.4MU administered

to 204 mothers who had acquired syphilis within the past year.[5] However, it remains difficult to prove all women actually acquired syphilis during the last year and were not just showing 'serological scars' [persistent low rapid plasma reagin (RPR) and positive Treponema pallidum hemagglutination assay (TPHA)], as is sometimes seen for years after a former, cured episode of syphilis. When such women with persistent low titres were excluded from the analysis of another study of 196 mothers with early stage syphilis, treatment with a single intramuscular injection of benzathine benylpenicillin 2.4MU did not prevent preterm birth, intrauterine death and congenital syphilis, when compared with no treatment.[2] However, after 2 injections one week apart, the neonatal outcome was favourable and comparable to 3 weekly injections.[2] After adjusting for the fact that some injections may have been given at longer intervals than 1 week and for the possibility that some women may have delivered before they had the full advantage of the treatment given, identical conclusions were reached in this study: treponemocidal activity of less than 3 weeks' duration (the estimated 'full action' equivalent of one injection of benzathine benzylpenicillin 2.4MU) was insufficient to protect the newborn from the devastating effects of the parasite. Unexpectedly, this insufficient protection was most pronounced when treatment was given early in pregnancy.

Therefore, as long as there are no further data on the efficacy of benzathine benzylpenicillin on the outcome of pregnancy, as a minimal approach, treatment with a single injection of benzathine benzylpenicillin is advised in those patients whose syphilis was acquired at 1 year or less, but it may be wise to add a second identical dose 1 week after the initial one. This extra dose is especially warranted when the exact duration of syphilis is unknown, or when patients are seen early in pregnancy. With these safety measures taken into consideration, screening and treatment should take place as early in pregnancy as possible.

Follow-up tests using the quantitative RPR or Venereal Disease Research Laboratory tests need to show a 4-fold decrease over less than 1 year to become negative eventually. During pregnancy, the rate of declining RPR titres is slower than outside pregnancy. Furthermore, the later treatment is given during pregnancy, the slower the rate of decline of the reagin tests. Even when pregnant patients receive adequate treatment, sporadic cases of congenital syphilis will develop.[2,6,7] One should bear in mind that some women will continue to have positive tests at a low titre (less than 1 : 8). Such weak titres, together with a positive TPHA or fluorescent treponemal antibody absorption (FTA-ABS), may indicate that this patient has had a former, cured syphilis infection, has acquired syphilis recently (and high titres have not developed yet) or may indicate treatment failure. If the RPR titre more than doubles again, relapse or re-infection has occurred and treatment should be reinstated. In these patients, an examination of the CSF to exclude neurosyphilis is indicated. Intensive efforts are needed to find and treat the sexual partners of these women, a task that is not easy to accomplish in pregnancy, as in some high risk areas secret sexual contacts during pregnancy are common, while the legal husband may even remain seronegative.[2]

A peculiar adverse effect of penicillin therapy, the Jarisch-Herxkeimer reaction, may occasionally be encountered during pregnancy. When it occurs during the second half of pregnancy, it may lead to preterm contractions and associated fetal distress. Of note, as the Jarisch-Herxheimer reaction only occurs when spirochetes are abundant, preterm birth or stillbirth should also be expected as a consequence of severe, untreated syphilis itself.[2] Penicillin allergy is reported in approximately 10% of pregnancies, but threatening allergic reactions are rare and only 30 to 40% of alleged allergic patients actually show positive skin tests. As long as there are no good and safe alternatives to penicillin in pregnancy, the treatment of preference has to be penicillin desensitisation followed by treatment with intravenous or intramuscular penicillin. If a skin test proves positive, the patient should be desensitised by oral administration of increasing doses of phenoxymethylpenicillin (penicillin V)

suspension according to a strict protocol.[8] The use of macrolides, such as erythromycin, has been shown to produce inferior results to penicillin and should to be discouraged. Treatment with ceftriaxone 250mg to 2g was effective in some studies, but treatment has to be administered for at least 5 (2g regimen) to 10 (250mg regimen) days.[9,10] Even in high doses of up to 3g, a single dose of ceftriaxone is insufficient for cure.[10] Thus, if ceftriaxone is chosen as an alternative treatment for syphilis in patients with penicillin allergy, multiple dose therapy should always be used.

2. Gonorrhoea

Where syphilis is prevalent, systematic screening with cervical culture for gonorrhoea is also obligatory. Although usually associated with a higher prevalence of syphilis, there may be situations where screening for gonorrhoea is warranted whether or not syphilis is present. We have calculated that screening is cost efficient when gonorrhoea prevalence is more than 1%.[2] Although some claim urethral swabs add little to the yield obtained with a cervical specimen, we advise to first swab the urethra and then the cervix with the same swab. Gonorrhoea is a most devastating infection during pregnancy, leading to a 4-fold increased risk of preterm delivery.[1] Whereas in most parts of the world penicillinase-producing strains preclude the use of penicillin, ampicillin and amoxycillin, in other areas, such as central South Africa, the rate of gonorrhoea has declined over the last 10 years, without penicillinase-producing strains of *Neisseria gonorrhoeae* (PPNG) emerging (van Straeten D, personal communication). Although treatment of uncomplicated gonorrhoea with benzylpenicillin is a tempting option in countries where treatment cost plays a pivotal role and there is good surveillance of both PPNG and chromosomally resistant *N. gonorrhoeae*, it is still ill-advised. Indeed, as seen in other countries with a previously low incidence of PPNG, this situation can change rapidly.[11] Chromosomal resistance continues to evolve and spread all over the world.

In most Western and Eastern countries, rates of gonorrhoea are falling, but the proportion of PPNG is rising. In Heidelberg, for example, PPNG represented 10% of the strains in one study.[12] According to some, a single dose of ceftriaxone 125mg is sufficient to treat uncomplicated gonorrhoea[13] but, notwithstanding the CDC guidelines that recommend the same 125mg regimen for pharyngeal or complicated forms, 250mg has been advised by others.[14] Given the serious risks of preterm birth and the 30% increased volume of distribution (Vd) during pregnancy,[15] a dose of 250mg should also be preferred for uncomplicated gonorrhoea during pregnancy. Adverse effects such as immediate type hypersensitivity are extremely rare.[16] Even though test of cure is not advised outside pregnancy, and can be omitted if concomitant therapy to cover *Chlamydia trachomatis* is given (see section 3), a control swab 4 weeks after treatment is strongly recommended in most other situations, given the devastating effect of un- or under-treated gonorrhoea on pregnancy. It also enables further STD screening, as concomitant chlamydial infection, syphilis, trichomonasis and/or HIV infection would compromise the pregnancy outcome even further. If the test of cure is positive, extended partner notification and treatment should be instigated, as well as re-treatment with a single intramuscular injection of ceftriaxone 250mg. When gonorrhoea is diagnosed and treated early in pregnancy, a repeat culture is warranted in the third trimester.

One single oral dose of ofloxacin 400mg or ciprofloxacin 500mg is extremely efficient in eradicating *N. gonorrhoeae* in non-pregnant women, but the use of these agents is contraindicated during pregnancy because of maturation defects in the joint cartilage of the neonate, with a risk of lifelong disabilities, analogous to those seen in experimental animals.[17] Although one study demonstrated an increased risk of 11.9% of congenital malformations after exposure to ofloxacin *in utero*,[18] accidental use of quinolones during pregnancy has not revealed these or other notorious adverse effects in human neonates, not even when used in the first trimester or in high doses.[19] It should also be men-

tioned that quinolone resistance against *N. gonorrhoeae* is rising rapidly in some parts of the world, already precluding its use for gonorrhoea in vast areas of South-East Asia.

Cefixime allows an oral equivalent of intramuscular ceftriaxone in the treatment of gonorrhoea, including PPNG. Cefixime serum concentrations, minimum inhibitory concentration (MIC) values and cure rates after a single oral dose of 400mg compared well with intramuscular ceftriaxone 250mg in 233 nonpregnant patients.[20] Furthermore, this treatment is considered safe during pregnancy and lactation, and can be viewed as the treatment of choice in pregnancy. A 400mg regimen is recommended[21] rather than the 800mg regimen, because of the lower likelihood of gastrointestinal adverse effects.[20]

In view of possible co-infection with *C. trachomatis*, which is suspected to occur in at least 25% of patients with gonorrhoea, treatment with a oral azithromycin is promising. Single doses of azithromycin 1g have produced 93 to 100% bacteriological cure rates for gonorrhoea.[22-24] During pregnancy, as well as in complicated cases of gonorrhoea, 2g regimens must be considered. However, gastrointestinal intolerance rates can be as high as 35% with the latter regimen and may even be higher during pregnancy. There are no specific data available from randomised trials on the safety of the use of azithromycin during pregnancy, but the drug has been used extensively during pregnancy without any notable adverse effect.

3. Chlamydia

Uncomplicated chlamydial urethritis or cervicitis must be treated with either erythromycin or azithromycin, as both tetracyclines and fluoroquinolones are contraindicated during pregnancy. Outside pregnancy, erythromycin base 500mg or erythromycin ethylsuccinate 800mg (both four times daily for 7 days) are slightly less efficient than azithromycin 1g, and the effect of the 7-day regimen depends entirely on full compliance.[4] As azythromycin can be applied as a single dose, it can be dispensed on site and its intake can be supervised. A single dose of less than 1g is less efficient in eradicating urethritis in men,[25,26] so single doses below 1g are also likely to be insufficient in pregnancy. If co-infection with gonorrhoea is a possibility, 1g may be insufficient during pregnancy. A single 2g dose produced high bacterial cure rates from all anatomical sites for both gonorrhoea and chlamydial infection in 370 of 374 and 17 of 17 patients, respectively.[22] In an attempt to prevent the frequent adverse effects, alternative regimens involving azythromycin 1g combined with cefixime 400mg have been used.[27] However, this combined regimen produced even more adverse effects than those reported after a single dose of azythromycin 2g. For lymphogranuloma venereum, caused by *C. trachomatis* serotypes L1 to L3, the same medication can be used as for chlamydial cervicitis, but longer therapy is required. According to CDC recommendations, test of cure for chlamydial infections is warranted, as well as repeat testing in the third trimester of pregnancy.

Despite its efficacy in pregnancy, concerns about the possible adverse effects or teratogenesis of azythromycin may preclude its unconditional use in pregnancy. However, no teratogenic effects were observed in reproduction studies in animals, and it has been awarded US Food and Drug Administration pregnancy rating category B status. At least two studies have shown a single 1g dose to be equivalent to erythromycin 2 g/day for 7 days in eradicating *C. trachomatis* during pregnancy, and there was no harm to the fetus in the 60 patients involved.[28,29] Numbers of pregnant women treated in published series are still limited. Nevertheless, the drug is in world-wide use now and no adverse effects for the fetus have been reported as yet.

As large scale studies on the safety of this drug during pregnancy will probably never be carried out, the attending physician will have to decide for him or herself whether or not the incomplete knowledge of fetal adverse effects outweighs the efficiency compared with alternative treatments during pregnancy. Although well-designed studies in pregnancy are scarce, and given the poor tolerability of erythromycin during pregnancy, we believe that present

knowledge is sufficiently confirmative to use single dose azythromycin in pregnancy for the treatment of chlamydial infections, particularly if concomitant gonorrhoea is present or suspected. One study provides evidence that amoxycillin is also efficient for treating chlamydial infections during pregnancy,[30] leading to the CDC recommendation to use it as a possible alternative.[4]

Because of the lesser impact of the infection on the course of pregnancy than syphilis and gonorrhoea, and the efficiency of the medication which is claimed to be virtually complete, many advocate that there is no need for test of cure. Only if complaints or symptoms of urethritis or cervicitis persist is there a need to retest for *C. trachomatis*, gonorrhoea, syphilis, trichomoniasis and HIV infection, as re-infection or concomitant infection may have occurred. On the other hand, when the prevalence of chlamydia is above 10%, test of cure and repeated screening of both treated and initially negative pregnant women may be advised,[31] and the CDC recommends test of cure in all pregnant women.

4. Chancroid

Chancroid is also very often a co-infection, or leads to co-infection, with other STDs, primarily HIV, herpes, syphilis and probably also chlamydia and gonorrhoea. Its causative organism, *Hemophilus ducreyi*, is extremely sensitive to ceftriaxone (single dose of 250mg), erythromycin (2 g/day for 7 days) or azythromycin (single oral 1g dose).[4] Cultures for *H. ducreyi* will become negative, but the specific culture technique is not widely available, is difficult to perform and is not very sensitive. Hence, the test of cure means demonstration of clinical and subjective improvement of the lesions after 1 week, and complete healing of the ulcers after 2 to 3 weeks. All recent sexual partners need to be treated as well, regardless of whether or not they are symptomatic. Fluoroquinolones, although effective for chancroid, are contraindicated in pregnancy.

5. Trichomonas

Trichomonas vaginalis is a parasite that causes vaginitis, urethritis and infection of the perigenital accessory glands. The drug of choice for trichomoniasisis the anti-anaerobic antibiotic metronidazole, by oral administered at a dosage of 500mg twice a day for 5 to 7 days. Alternatively, oral metronidazole can be given as a single 2g dose, but gastrointestinal tolerance may be a problem. In general, the oral regimens are preferred over vaginal applications, as the accessory glands and urine are often infected and adequate metronidazole concentrations may not be reached with the latter route. Therefore, neither ovulae containing metronidazole nor low dose gels of metronidazole are advisable for treatment of vaginal trichomoniasis in pregnancy, except when treatment is in the first trimester. The latter treatment in the first trimester by vaginal application of metronidazole instead of oral, stems from the fear of teratogenesis in the beginning of pregnancy.

As earlier studies claimed possible carcinogenic and teratogenic effects in mice, concerns about the safety of metronidazole use in pregnancy make some physicians and patients reluctant to use it for a condition that was considered to be a banal cause of vaginitis. However, *T. vaginalis* infection is associated with preterm delivery and preterm rupture of the fetal membranes and therefore needs to be treated adequately.[32] Furthermore, as with many other STDs, co-infection with other genital pathogens is common, and the bacterial vaginal flora is often severely disturbed, increasing the likelihood of preterm delivery yet further.[33] Recent reanalysis of the earlier studies and a review of the currently available information on the adverse effects of the use of metronidazole in human pregnancy provide reassurance, and allow the use of oral metronidazole in the second and third trimester of pregnancy. If the infection is symptomatic, use of vaginal ovules is also permissible in the first trimester.[34]

Tinidazol (2g once) and ornidazol (1.5g once) are effective in eradicating *T. vaginalis* and better tolerated than metronidazole, but safety data dur-

ing pregnancy are too sparse to legitimate their use in pregnancy.

6. Abnormal Vaginal Flora and Bacterial Vaginosis

Although bacterial vaginosis is not usually classified as an STD, its relationship with sexual activity cannot be denied. Bacterial vaginosis becomes more frequent after sexual debut and increases with the number of sexual partners, and the symptoms become most obvious after unprotected vaginal intercourse.[35] Recent studies found associations between bacterial vaginosis and other STDs, such as trichomoniasis, chlamydial infection, gonorrhoea, syphilis and HIV infection.[35,36] We have previously pointed out that these STDs are often associated with severely disturbed bacterial flora (absence of lactobacilli), but plead for cautiousness in calling any disturbed vaginal flora bacterial vaginosis.[32] Bacterial vaginosis in its original semantics means an overgrowth by *Gardnerella vaginalis* and anaerobic bacteria, such as Bacteroides, Prevotella, peptostreptococci and Mobiluncus spp., leading to fishy odor, thin discharge, increased pH, and decreased or absent lactobacillary morphotypes and clue cells on microscopy. When other clinical infections such as cervicitis, aerobic vaginitis or certain STDs cause the vaginal flora to become abnormal,[37] one should not call this condition bacterial vaginosis, unless the above criteria of anaerobic bacteriosis are present.

Confused use of the term bacterial vaginosis can lead to less-than-optimal treatment being instituted, and may lead to the peculiar finding that although bacterial vaginosis is associated with preterm birth, successful treatment cures most cases of 'bacterial vaginosis' but does not always prevent this complication of preterm birth.[38] Not every woman with bacterial vaginosis is at risk of pregnancy complications, but those with associated infections or non-infectious prematurity risks, such as low maternal weight, previous preterm delivery, and concomitant infection with mycoplasma or bacteroides, are at risk.[38] Therefore, bacterial vaginosis and abnormal bacterial flora may both be seen as markers that require further investigation of the prematurity risk and warrant appropriate treatment in some subgroups of patients to prevent complications during the pregnancy. Screening and treatment should be initiated as early as in the first trimester, as miscarriage and second trimester pregnancy losses also seem to correlate with the finding of bacterial vaginosis and disturbed flora.[32,38,39]

Treatment of bacterial vaginosis is still under discussion. Both metronidazole and clindamycin eradicate 85% of bacterial vaginosis, but up to 40 to 80% recurrence rates can occur within 6 months.[40,41] This high recurrence rate cannot be ameliorated by treating the woman's sexual partner.[4,42,43] Therefore, both test of cure and follow-up examinations are mandatory during pregnancy. The use of acidifying vaginal products and the insertion of lactobacilli into the vagina in order to prevent recurrences after acute treatment have not been examined thoroughly yet, but preliminary results seem promising.[44,45] For acute treatment, metronidazole can be administered as a single oral dose of 2g, or orally at a dose of 500mg twice daily for 5 days.[46] The CDC recommends metronidazole 250mg 3 times daily for 5 to 7 days, in order to minimise possible fetal adverse effects.[4] However, it is anything but logical to undertreat during pregnancy, as the increased Vd, 15% treatment failure rate and the high recurrence rate would argue more for an increased rather than a decreased dose, particularly if there is an additional risk of preterm delivery. Vaginal treatment with either metronidazole (500mg ovules daily for 5 days or 0.75% gel for 7 days) or clindamycin (5g daily of 2% cream for 5 days) is also possible, but prevention of preterm birth is less well proven with the use of local administration and, therefore, oral administration with either metronidazole or clindamycin is currently advised.[46]

7. Conclusion

Testing and treating for STDs is different in pregnant women compared with nonpregnant women. First of all, routine search for most STDs is warranted during the early stages of pregnancy, especially when prevalence is known or suspected

to be high. A special reason for this is the potential harm of most STDs for the pregnancy, with chorioamnionitis, fetal infection, stillbirth and preterm delivery being the most feared complications. Secondly, partner notification and treatment is important to prevent re-infection, but one has to realise this may be more delicate and unsuccessful because of pregnancy. Thirdly, one has to search for the most suitable medication which combines maximal efficiency and compliance to therapy with lack of teratogenicity. Finally, rather than risking insufficient treatment because of fears of alleged and often remote adverse effects for the fetus, often a higher dose of medication is desirable during pregnancy.

As a final remark, it must be remembered that the occurrence of one STD must make any clinician suspicious of possible concomitant STD pathogens. HIV must be feared in particular, as African data clearly show that any STD, especially the ulcerative ones such as herpes, chancroid and syphilis, but also gonorrhoea, chlamydial infection and trichomonasis, facilitate the transmission of HIV.[47] Recent data provide evidence that abnormal vaginal flora such as bacterial vaginosis is also associated with an increased risk for HIV transmission.[48]

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References

1. Donders GGG, Desmyter J, De Wet GH, et al. The association of gonorrhoea and syphilis with premature birth and low birth weight. Genitourin Med 1993; 69: 98-101
2. Donders GGG, Desmyter J, Hooft P, et al. Apparent failure of one injection of benzathine penicillin G for syphilis during pregnancy in human immunodeficiency virus-negative African women. Sex Transm Dis 1997; 24: 96-101
3. Stray-Pedersen B. Cost-benefit analysis of a prenatal preventive programme against congenital syphilis. NIPH Ann 1980; 48: 57-66
4. Centers for Disease Control and Prevention. Guidelines and treatment of sexually transmitted diseases: MMWR recommendations and report. Atlanta (GA): US Department of Health and Human Services, 1998
5. Alexander JM, Sheffield JS, Sanchez PJ, et al. Efficacy of treatment for syphilis in pregnancy. Obstet Gynecol 1999; 93: 5-8
6. Conover CS, Rend CA, Miler Jr GB, et al. Congenital syphilis after treatment of maternal syphilis with a penicillin regimen exceeding CDC guidelines. Infect Dis Obstet Gynecol 1998; 6: 134-7
7. McFarlin BL, Bottoms SF, Dock BS, et al. Epidemic syphilis: maternal factors associated with congenital infection. Am J Obstet Gynecol 1994; 70: 535-40
8. Wendel Jr GD, Sark BJ, Jamison RB, et al. Penicillin allergy and desensitization in serious infections in pregnancy. N Engl J Med 1985; 312: 1229-32
9. Hook EW, Roddy RE, Handsfield HH. Ceftriaxone for incubating and early syphilis. J Infect Dis 1988; 158: 881-4
10. Moorthy TT, Lee C-T, Lin K-B, et al. Ceftriaxone for treatment of primary syphilis in men: a preliminary study. Sex Transm Dis 1987; 14: 116-8
11. Lind I, Arborio M, Bentzon MW, et al. The epidemiology of Neisseria gonorrhoeae isolates in Dakar, Sénégal 1982-1986: antimicrobial resistance, auxotypes and plasmid profiles. Genitourin Med 1991; 67: 107-13
12. Kohl PK, Tu Y, Hostalek U, et al. Activity of cefixime against Neisseria gonorrhoeae. J Eur Acad Dermatol Venerol 1995; 4: 155-9
13. Mandell GL, Douglas Jr RG, Bennett JE, et al. Treatment of sexually transmitted diseases. In: Mandell GL, Douglas RG, Bennett JE, editors. Principles and practice of infectious diseases: antimicrobial therapy 1996/1997. New York (NY): Churchill Livingstone, 1996: 92-6
14. Judson FN. Treatment of uncomplicated gonorrhea with ceftriaxone: a review. Sex Transm Dis 1986; 13: 199-202
15. Ueland K, Metcalfe J. Circulatory changes in pregnancy. Clin Obstet Gynecol 1975; 18: 41-56
16. Zishka PA, Douglas JM. Immediate hypersensitivity reaction to single-dose parenteral ceftriaxone therapy for gonorrhea. Sex Transm Dis 1992; 18: 26-7
17. Ingham B, Brentnall DW, Dale EA, et al. Arthropathy induced by antibacterial fused N-alkyl-4-pyridone-3-carboxylic acids. Toxicol Lett 1977; 6: 21-6
18. Schaefer C, Amoura-Elefant E, Vial T, et al. Pregnancy outcome after prenatal quinolone exposure: evaluation of a case registry of the European Network of Teratology Information Services 5 (ENTIS). Eur J Obstet Gynecol Obstet Reprod Biol 1996; 69: 83-9
19. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. Antimicrob Agents Chemother 1998; 42: 1336-9
20. Handsfield HH, McCormack WM, Hook III EW, et al. A comparison of single dose cefixime with ceftriaxone as treatment for uncomplicated gonorrhea. N Engl J Med 1991; 325: 1337-41
21. Verdon MS, Douglas JM, Wiggins SD, et al. Treatment of uncomplicated gonorrhea with single doses of 200 mg cefixime. Sex Transm Dis 1993; 20: 290-3
22. Handsfield HH, Dalu ZA, Martin DH, et al. Azythromycin Gonorrhoea study group: multicenter trial of single-dose azythromycin vs ceftriaxone in the treatment of uncomplicated gonorrhoea. Sex Transm Dis 1994; 21 107-11
23. Waugh MA. Open study of the safety and efficacy of a single oral dose of azithromycin for the treatment of uncomplicated gonorrhea in men and women. J Antimicrob Chemother 1993; 31 Suppl. E: 193-8
24. Steingrimsson O, Olafsson JH, Thorainsson H, et al. Single dose azithromycin treatment of gonorrhea and infection caused by C trachomatis and U urealyticum in men. Sex Transm Dis 1994; 21: 43-6
25. Martin DH, Mroczkowski TF, Dalu ZA, et al. A controlled trial of a single dose of azythromycin for the treatment of

Chlamydial urethritis and cervicitis. N Engl J Med 1992; 327: 921-5
26. Worskowski KA, Johnson RB, Verdon M, et al. Azithromycin in chlamydial urethritis [letter]. JAMA 1993; 270: 1934-5
27. Worskowski KA, Hook EW, Handsfield HH. Single dose cefixime plus azithromycin in the treatment of uncomplicated gonorrhoea and chlamydial infection [abstract]. 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy; 1992 Oct 11-14; Anaheim (CA), 340
28. Edwards M, Rainwater K, Carter S, et al. Comparison of azythromycin and erythromycin for chlamydia cervicitis in pregnancy [abstract]. Am J Obstet Gynecol 1994; 84: 61-3
29. Bush MR, Rosa C. Azythromycin and erythromycin in the treatment of cervical chlamydial infection during pregnancy. Obstet Gynecol 1994; 84: 61-3
30. Crombleholme WR, Schachter J, Grossman M, et al. Amoxicillin therapy for Chlamydia trachomatis in pregnancy. Am J Obstet Gynecol 1990; 75: 752-6
31. D'Allaire, Huddleston JF, Graves WL, et al. Initial and repeat screening for Chlamydia trachomatis during pregnancy. Infect Dis Obstet Gynecol 1998; 6: 116-22
32. McGregor JA, French JI, Parker R, et al. Prevention of premature birth by screening and treatment for common genital tract infections. Am J Obstet Gynecol 1995; 173: 157-67
33. Donders GGG, De Wet GH, Hooft P, et al. Lactobacilli in Pap smears, genital infection and pregnancy. Am J Perinatol 1993; 3: 17-25
34. Struthers BJ. Metronidazole appears not to be a human teratogen: review of the literature. Infect Dis Obstet Gynecol 1997; 5: 326-35
35. Hart G. Risk profiles and epidemiologic interrelationships of sexually transmitted diseases. Sex Transm Dis 1993; 20: 126-36
36. Simoes JA, Camargo RP, Giraldo PC, et al. Association between prenatal complications and bacterial vaginosis in Brazilian pregnant women. Second International Meeting on Bacterial Vaginosis; 1998 Sept 17-19; Aspen (CO), 30
37. Donders GGG. Microscopy of the bacterial vaginal flora on fresh vaginal smears. Infect Dis Obstet Gynecol 1999; 7: 177-9
38. Donders GGG. Bacterial vaginosis during pregnancy: screen and treat [editorial]. Eur J Obstet Gynecol Reprod Med 1999; 83: 1-4
39. Hay PE, Lamont RF, Taylor-Robinson, et al. Abnormal bacterial flora colonisation of the genital tract and subsequent delivery and late miscarriage. BMJ 1994; 308: 295-8
40. Donders GGG, Van Bulck B, Caudron J, et al. Bacterial vaginosis and Mycoplasmata increase the risk of spontaneous first trimester abortion. Am J Obstet Gynecol. In press
41. Boris J, Pahlson C, Larsson P-G. Six years observation after successful treatment of bacterial vaginosis. Infect Dis Obstet Gynecol 1997; 5: 297-302
42. Cook RL, Relondo-Lopez V, Schmitt C, et al. Clinical, microbiological and biochemical factors in recurrent bacterial vaginosis. J Clin Microbiol 1992; 30: 870-7
43. Moi H, Erkkola R, Jerve F, et al. Should male consorts of women with bacterial vaginosis be treated? Genitourin Med 1989; 65: 263-8
44. Hallen A, Jarstrand C, Pahlson C. Treatment of bacterial vaginosis with lactobacilli. Sex Transm Dis 1992; 19: 146-8
45. Hillier S, Krohn MA, Meyn L, et al. Recolonisation of the vagina with an exogenous strain of Lactobacillus crispatus. Second International Meeting on Bacterial Vaginosis; 1998 Sept 17-19; Aspen (CO), 18
46. Lugo-Miro VI, Green M, Mazur L. Comparison of different metronidazole therapeutic regimens for bacterial vaginosis: a meta-analysis. JAMA 1992; 268: 92-5
47. Dickerson MC, Johnston J, Delea TE, et al. The causal role for genital ulcer disease as a risk factor for transmission of human immunodeficiency virus. Sex Transm Dis 1996; 23 (5): 429-40
48. Sewankambo N, Gray RH, Wawer MJ, et al. HIV-1 infection associated with abnormal vaginal flora morphology and bacterial vaginosis. Lancet 1997; 350: 546-50

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