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Treatment of *Chlamydia trachomatis* Infections in Pregnant Women

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Contents

Abstract

The intent of this article is to provide an overview of the epidemiology and pharmacotherapy, including cost analyses, of *Chlamydia trachomatis* infections in pregnant women. Chlamydia is a common sexually transmitted infection. For pregnant women, there are concerns both for the mother (post-partum endometritis, horizontal transmission) and the newborn (conjunctivitis, delayed pneumonia). Therapeutic options are restricted because of the fetus and include multi-day treatment with erythromycin, amoxicillin, clindamycin or single dose azithromycin. Clinical cure rates with these options are 86, 92, 93 and 95%, respectively.

Pharmacoeconomic analyses have been conducted to determine if the initial increase in acquisition cost of azithromycin (approximately 3-fold higher than erythromycin or amoxicillin) is offset by improvement in compliance and drug efficacy. Clindamycin has received little attention because of its expense (4-fold more than azithromycin). Analyses have been retrospective. As models incorporate more complications of failure to cure, azithromycin increasingly becomes more cost effective and is our recommended treatment.

1. Obstetric Overview

1.1 General Problem

Chlamydia trachomatis is the most common sexually transmitted pathogen and is the most likely to be found in an obstetric population, with 2 to 20% of pregnant women infected.[1] As a consequence of its high prevalence, *C. trachomatis* infections result in significant morbidity with concomitant social and economic costs. Left untreated, an affected pregnant patient may (i) pass the organism to her child at delivery, (ii) develop post partum endometritis - salpingitis,[2] (iii) contribute to horizontal spread throughout the community and (iv) experience possible adverse obstetric outcomes such as preterm delivery, low birth weight or premature rupture of the membranes.[3-6] Non-pregnant women may experience pelvic inflammatory disease (10 to 40%)[7] and its sequelae of infertility and ectopic pregnancy.[8] While not an immediate concern in a pregnant patient, persistent infection beyond the peripartum period may result in any or all these consequences.

1.2 Epidemiology

A major increase in reported chlamydial infection occurred between 1984 (3.2 cases per 100 000) and 1994 (188 cases per 100 000), probably reflecting improved screening and reporting.[7] Subsequent modest declines after 1994 have been reported, usually in settings where well established screening programs are in place.[9,10]

Infection occurs most often among younger women, generally those who are sexually active and below the age of 25 years.[7] Prevalence is higher among those who are unmarried, nulliparous, of lower socio-economic status and have multiple sexual partners or have concurrent *Neisseria gonorrhoea* infection.[7,11] Recurrent infection also has been found to be associated with similar risk factors.[12] The mainstay for case-finding during pregnancy is screening. While universal testing may not be appropriate, certainly women with the above mentioned risk factors should be screened.

1.3 Diagnosis

Until recently, culture has been considered the 'gold standard' for the laboratory diagnosis of chlamydial infections. Although more expensive, properly performed cultures are more sensitive than antigen detection by enzyme immunoassay (EIA) and probe detection of chlamydia specific genetic material in clinical specimens.[13] More recently nucleic acid amplification tests have been developed, including polymerase chain reaction (PCR), ligase chain reaction (LCR) and transcription mediated amplification (TMA). The first two are DNA based whereas the latter is based on ribosomal RNA. All of these systems are more sensitive than culture and have very high specificities.[14] More recently, nontraditional specimens such as urine have been found to identify infected individuals. Availability of urine-based tests opens up the possibility of widespread population based screening for *C. trachomatis* as urethral swabs in men and pelvic examinations in women are no longer required.[13]

However, when directly compared, endocervical specimens appear to be modestly more sensitive than urine specimens for the detection of *C. trachomatis* in women.[15] Therefore, if a woman needs a pelvic examination for other indications, an endocervical specimen would be preferred over a urine specimen. This would apply to most pregnant women.

1.4 Perinatal Transmission

For the obstetrician, perinatal transmission is a significant concern. Vertical transmission of *C. trachomatis* generally occurs during labour and delivery with a frequency varying from 23 to 70%.[1,16,17] Prevalence of neonatal conjunctivitis, 11 to 50%, and neonatal pneumonia, 3 to 16%, have been reported among infants exposed at birth.[17-19] These complications are easily avoided through screening all high risk pregnant women and treating those infected to prevent unnecessary infectious morbidity in their neonates.

1.5 Therapeutic Considerations

According to the recently published Centers of Disease Control sexually transmitted diseases treatment guidelines, erythromycin base (500mg orally 4 times daily for 7 days) and amoxicillin (500mg orally 3 times daily for 7 days) are the drugs of choice for treatment of chlamydial infections in pregnant women.[20] Azithromycin (1g orally as a single dose) is listed as an alternate choice. This latter drug has a long tissue half-life of approximately 3 days[21] and is the only single dose treatment available. Others recommend sulfamethoxazole during the first and second trimester.[7] Doxycycline, the most commonly used antibacterial to treat chlamydial infections in men and non-pregnant women is not used in pregnant women. Neither is ofloxacin, the first of the fluoroquinolones found to be effective for chlamydial infection.

Concerns about cost, tolerance, efficacy, compliance, safety to the fetus, partner treatment, possible reinfection and disease sequelae all need to be considered when treating chlamydial infection. These issues are addressed in this review with the goal of enabling practitioners to rationally select treatment options for themselves. This review is based on a Medline search of English language articles from 1966 through February 1999 concerning treatment of *C. trachomatis* in pregnancy. Search words included chlamydia, antibacterial treatment and pregnancy. Additional articles were found among references provided by the papers identified in the computer search.

2. Antibacterial Selection

2.1 Tolerance

Antibacterial tolerance among pregnant women is a significant issue, especially gastrointestinal (GI) adverse effects. Generally these are minor, but may significantly decrease compliance, especially in the first trimester. The incidences of adverse effects for erythromycin base, amoxicillin, clindamycin and azithromycin are summarised in table I. The most prominent adverse effects are gastrointestinal and include nausea, vomiting, abdominal cramps or pain, and diarrhoea. Nongastrointestinal adverse effects, including rash, itching or allergy are generally not reported to occur in more than 4% of treated patients for each reviewed agent.[22-24] GI adverse effects are more common for erythromycin (13 to 100%, mean 37%)[22-30] as detailed in table I and confirmed by a meta-analysis of erythromycin and amoxicillin use in pregnancy.[32] In one study, 30% of patients taking erythromycin had their doses reduced by half because of intolerance.[29] GI adverse effects for the other 3 drugs were as follows: amoxicillin [22-26] (6 to 16%, mean 11%), clindamycin (10%)[25,27] and azithromycin (0 to 17%, mean 11%).[28-31] The findings for azithromycin have been confirmed by a large, prospective study of this drug alone, which demonstrated overall adverse effects in 5% of 147 patients.[33] With azithromycin, pregnant women, like non-pregnant patients, experience modest levels of intolerance, which are primarily mild to moderate.[34]

Table I. Symptoms reported with antibacterials for treatment of *Chlamydia trachomatis*

Antibacterial agent	Gastrointestinal adverse effects (%)	Reference
Amoxicillin	8/93 (9)	22
Erythromycin	13/100 (13)	
Amoxicillin	16/100 (16)	23
Erythromycin	48/99 (49)	
Amoxicillin	5/65 (8)	24
Erythromycin	30/65 (46)	
Amoxicillin	3/55 (6)	25
Erythromycin	13/53 (25)	
Clindamycin	5/52 (10)	
Amoxicillin	5/39 (13)	26
Erythromycin	12/38 (32)	
Clindamycin	4/40 (10)	27
Erythromycin	9/39 (23)	
Azithromycin	5/42 (12)	28
Erythromycin	25/43 (58)	
Azithromycin	0/15 (0)	29
Erythromycin	15/15 (100)	
Azithromycin	4/27 (15)	30
Erythromycin	12/21 (57)	
Azithromycin	NR (17)	31
Erythromycin	NR (45)	

NR = not reported.

2.2 Compliance

2.2.1 Associated Factors

In general, the failure to complete a course of medication is a greater concern during pregnancy because the consequences of treatment failure affect the fetus and/or infant as well as the mother. One study found that among non-pregnant patients self-reported noncompliance rates (40%) are substantially lower than electronically measured rates (70%).[35] These rates were determined by using medication bottles with computer chips in the cap which documented the number of times the bottle was opened. Factors associated with noncompliance have been evaluated in obstetric patients.[36] These include younger age and GI adverse effects.

Noncompliance may also include a delay in or failure to fill a prescription, for a variety of reasons including cost, and perhaps, a reluctance to take pills. In cited trials, the medication has generally been provided so there is no way to estimate the extent of this problem in practice, but it is almost certainly very significant. One study evaluating outpatient therapy for pelvic inflammatory disease found that 28% of patients did not fill their prescription.[37] For this group the most frequent reasons given for not filling the prescription were cost (38%) and feeling better (25%).[37]

Counselling would be appropriate to motivate the patient in all circumstances to ensure compliance, both in filling and taking medication. The quality of the physician–patient relationship is important in improving compliance.[38]

2.2.2 Influence of Pregnancy

Compliance among pregnant women has been evaluated in numerous prospective comparative studies, as summarised in table II. Completion of erythromycin therapy was recorded for 54 to 89% (mean 80%).[22-25,28,30,31] This is far less than reported for amoxicillin, 85 to 99% (mean 95%),[22-25] clindamycin 92%[25] or azithromycin, 93 to 100% (mean 96%).[28,30,31] In one study,[30] two noncompliant patients assigned to azithromycin failed to participate after randomisation. If they are excluded from analysis, reported compliance for azithromycin would be 99%. This is nearly the 100% compliance for azithromycin one would expect for directly observed therapy,[7] and the compliance level we found in our clinical trial.[33]

Table II. Compliance of pregnant patients in completing antibacterial therapy

Antibacterial	Completion of therapy (%)	Reference
Amoxicillin	55/65 (85)	24
Erythromycin	47/65 (72)	
Amoxicillin	91/93 (98)	22
Erythromycin	87/100 (87)	
Amoxicillin	99/100 (99)	23
Erythromycin	87/99 (88)	
Amoxicillin	53/55 (96)	25
Erythromycin	47/53 (89)	
Clindamycin	48/52 (92)	
Azithromycin	25/27 (93)	30
Erythromycin	15/21 (71)	
Azithromycin	41/42 (98)	28
Erythromycin	23/43 (54)	
Azithromycin	NR (100)	31
Erythromycin	NR (61)	

NR = not reported.

3. Efficacy

Bacteriological efficacy among pregnant women with *C. trachomatis* infection has been assessed by means of a test of cure, generally done between 2 and 6 weeks after initiating treatment. Trial results performed in pregnant women are summarised in table III. Erythromycin had a cure rate of 72 to 95% (mean 86%),[22-30,31,39] clindamycin 90 to 95% (mean 92%),[25,27] amoxicillin, 80 to 100% (mean 93%)[22-26] and azithromycin, 88 to 100% (mean 95%).[28-30,31,39] A published meta-analysis of amoxicillin versus erythromycin found amoxicillin to be more effective.[32] Other meta-analyses in pregnant women have not been done. However, our experience with azithromycin in an open trial[33] is comparable with those summarised in table III. Azithromycin would appear to be at least as effective if not slightly more effective than amoxicillin and significantly more effective than erythromycin. Better compliance is the most likely explanation for these results. Data on clindamycin are even more limited, precluding meaningful analysis.

Treatment failure need not reflect only failure to eradicate chlamydia, since reinfection may have

occurred even within the 2- to 6-week interval often used for tests of cure. In our experience, approximately half the failures may have been because of a reinfection.[33] Within the same pregnancy, reinfection in 17% of a high risk population has been documented.[40] Another study, evaluating women with positive tests for chlamydia obtained prior to 20 weeks, found 32% to have a subsequent positive test.[41] Based on these observations, we concur that tests of cure are desirable in pregnant women and that a third trimester test should be considered.[42]

4. Partner Concerns

Successful treatment of *C. trachomatis* infections in pregnant women requires involvement of the sexual partner. Many of the previously mentioned concerns about tolerance and compliance are valid for the partner as well as the patient and perhaps even more so. Unless the medication is provided free of charge, antibacterial cost may also limit successful partner treatment. Unfortunately, the patient may not inform the partner or the partner may not act on the information concerning infection by seeking treatment. It has been shown that if public health departments can develop an effective partner notification strategy, reductions in reinfection will result.[43] The alternate strategy, treatment of the partner by giving the woman a prescription to take home for her partner, has also resulted in fewer reinfections, at least in non-pregnant women.[44] In New Orleans, giving women doxycycline to take home to their partners appears to be effective.[45] This will prevent infectious sequelae. Partner education concerning general prevention of sexually transmitted infections through condom use is also advised.

Table III. Therapeutic efficacy of antibacterial treatment of *Chlamydia trachomatis* during pregnancy, measured by test of cure

Antibacterial	Bacteriological cure rate (%)	Reference
Amoxicillin	28/34 (80)	26
Erythromycin	27/32 (84)	
Amoxicillin	55/65 (85)	24
Erythromycin	47/65 (72)	
Amoxicillin	100/100 (100)	23
Erythromycin	87/99 (88)	
Amoxicillin	50/55 (91)	25
Erythromycin	45/53 (85)	
Clindamycin	47/52 (90)	
Amoxicillin	63/64 (98)	22
Erythromycin	55/58 (95)	
Clindamycin	38/40 (95)	27
Erythromycin	30/34 (88)	
Azithromycin	21/22 (96)	30
Erythromycin	16/20 (80)	
Azithromycin	15/15 (100)	29
Erythromycin	14/15 (93)	
Azithromycin	NR (91)	31
Erythromycin	NR (77)	
Azithromycin	39/42 (88)	28
Erythromycin	41/43 (93)	
Azithromycin	15/16 (94)	39
Erythromycin	12/15 (80)	

NR = not reported.

5. Cost Effectiveness

Relative cost effectiveness of different treatment approaches is a significant issue and one that must be addressed. Unfortunately, formal evaluation among pregnant patients has received little attention. Substantial data are available to evaluate cost, including costs of acquisition as well as infectious sequelae. Costs of failed treatment and infectious morbidity of both mother and infant must also be considered. If a public health programme is available for treatment, then costs of treatment must include not only the antibacterial costs, but those of case management and administration which are more difficult to assess.

Sample cost data indicate that the acquisition cost of azithromycin is nearly 3 times more than either amoxicillin or erythromycin in the US, which are approximately the same charge.[46,47] Clindamycin is over 10 times as expensive as amoxicillin or erythromycin.[46] This was confirmed by our own survey in New Orleans (table IV).

Available pharmacoeconomic studies have addressed single dose azithromycin and erythromycin or doxycycline for treating non-pregnant women.[47-50]

Table IV. Cost of antibacterials for treating chlamydial infection in pregnancy. New Orleans, Louisiana (survey of 4 pharmacy retail price quotes, March 1999)

Antibacterial treatment (duration)	Purchase cost ($US)	
	average	range
Erythromycin 500mg 4 times daily (7 days)	12.76	10.49-16.69
Amoxicillin 500mg 3 times daily (7 days)	10.88	7.35-13.69
Azithromycin 1g (single dose)	34.23	30.89-38.98
Clindamycin 450mg 4 times daily (14 days)	146.86	84.45-206.94

Studies have generally concluded that azithromycin is a cost-effective strategy.[50] The increase in compliance of single dose treatment over that of a 7-day course is likely the most important factor in the economic analysis. Moreover, the consequences of infection are not uniformly considered with only a single report including some costs relating to neonatal infectious sequelae.[48]

The study by Nuovo et al.[47] evaluated erythromycin and azithromycin, (along with antibacterials not used in pregnancy, i.e. tetracycline, doxycycline and ofloxacin) using decision analysis.[47] Only non-pregnant patients were considered. The authors used published clinical and economic evaluations, in addition to health insurance company or state health reports. The authors concluded that azithromycin was more cost-effective. A significant limitation of this study was the exclusion of late complications of pelvic inflammatory disease, such as infertility, ectopic pregnancy and chronic pelvic pain, and problems subsequent to infection in pregnancy, including neonatal conjunctivitis and pneumonia. Costs of treating sexual partners were also not included. Based on a sensitivity analysis, the authors concluded that a 3% improvement in cure rate for azithromycin over the other evaluated drugs was needed to justify using the more expensive agent.[47]

Haddix et al.,[49] also evaluated the relative cost efficacy of azithromycin and doxycycline. Although the latter is not used in pregnancy, the analysis is illuminating. The authors did include in their analysis the cost of tests of cure, which would be appropriate to any consideration of cost efficacy in pregnant women. They also allowed for differences between a public clinic and a private healthcare system, where the latter incurs expenses of acute pelvic inflammatory disease. These authors used results from the literature for efficacy and compliance.[49] Costs of pelvic inflammatory disease and its sequelae were considered, but perinatal complications were specifically excluded. When only confirmed cases were evaluated, use of azithromycin resulted in substantial savings to the healthcare system. For publicly-funded programmes where the cost of complications are not borne by the programme, azithromycin was more expensive. However, these savings are artificial, as other sections of the healthcare system must absorb the cost.

Another model presented in this article demonstrated increasing savings with azithromycin as compliance with other drugs decreased.[49] Here the authors limited their analysis to direct medical costs only. The consequences of secondary transmission to other sexual partners and influence of maternal-neonatal infection were not considered.

Marra et al,[50] using assumptions made by Haddix et al,[49] evaluated the cost effectiveness of doxycycline and azithromycin in non-pregnant women. For confirmed cases, azithromycin achieved lower overall cost. The limitations of this study are the same as the prior report of Haddix et al.[49]

Magid et al.[48] also compared azithromycin and doxycycline use in non-pregnant women for treatment of chlamydial infection. Their analysis and assumptions were similar to Haddix et al.[49] and Marra et al.[50] However, they did consider the consequences of secondary transmission of infection, adverse events stemming from drug use, and most importantly, sequelae to children born to infected mothers. These authors found cost savings in 1993 of $US39.56 per patient with the use of azithromycin.[48] Wholesale drug costs were used in this analysis. As with other studies, the authors developed a sensitivity model which revealed increased savings for the azithromycin strategy as the failure rates for doxycycline increased.

The only paper dealing with cost effectiveness of treatment during pregnancy is by Hueston and Lenhart.[46] They considered 4 antibacterial agents: amoxicillin, erythromycin, clindamycin and azithromycin. Using retail drug costs and cure rates drawn from the literature, a decision analysis was constructed looking at costs which included the cost of retreatment (with a different antibacterial) or recurrent infections. While the authors estimated overall failure rates after retreatment, they did not consider the remote costs of failure to cure. Costs of drug reactions or complications and the subsequent office revisit were also omitted. Antibacterial effectiveness was established from a literature review of treated pregnant women, with the exception of azithromycin. Here, data were drawn from non-pregnant women and the estimated effectiveness was 94%. The least expensive combination was amoxicillin, with erythromycin used for treatment failure. When the costs of improving the cure rate were considered, amoxicillin with azithromycin as second line therapy was the most economic.[46] The actual cost difference between using amoxicillin or azithromycin from Hueston and Lenhart's study[46] was approximately $US15 per patient. The incremental costs of amoxicillin with follow-up azithromycin versus the reverse was a difference of less than $US2 in order to improve the cure rate by 1 per 1000 patients.

No study has considered the potential obstetric problems which have been attributed to chlamydial infection. These include premature rupture of the membranes, preterm delivery or low birth weight. However, the statistics are conflicting.[3-6,51-53] Trials that have reported improvement of pregnancy outcome with treatment have used erythromycin over an extended period of time. However, use of this antibacterial may also influence other vaginal flora. Therefore, reported improvement in pregnancy outcome may reflect more than chlamydial treatment alone. Nevertheless, even a minor benefit in the prevalence of low birth weight would have great economic consequences. Analysis would again favour use of the most effective antibacterial against chlamydia.

6. Conclusion

Based on the available data we believe it is reasonably clear that the best choices for treating chlamydial infections in pregnant women are amoxicillin or azithromycin. Unfortunately, there are no direct comparative studies of these two approaches. In the absence of adequate data, we believe that the optimal choice depends upon the patient. Though the acquisition costs of azithromycin are greater than amoxicillin we feel that the former is a better choice for potentially noncompliant pregnant women such as adolescents.

Amoxicillin must be taken 3 times daily for a week and it is a bacteriostatic drug against chlamydia whereas the macrolide and tetracycline class drugs have bacteriocidal activity.[54] Therefore, compliance may be a much more important issue for the penicillins compared with the other two classes of drug, that is, it may well be that missing 30 to 40% of the doses for one of the bacteriocidal drugs would have a relatively smaller effect than missing a similar number of doses of a bacteriostatic drug. Head-to-head comparisons of the drugs would be necessary in order to prove this hypothesis.

Another factor is that given the higher cost of azithromycin women may be less likely to fill their prescriptions. Therefore, in order to exploit the compliance advantage of azithromycin it should be administered by directly observed therapy, which would require that the healthcare provider either supply the medication or ask patients to obtain it from the pharmacy and then return to the clinic for treatment. Obviously, the latter is less efficient, but in our experience is feasible. Amoxicillin is a reasonable choice for the patient who is deemed to be likely to comply with treatment. If amoxicillin is to be provided or prescribed, we believe it is critically important that patients be adequately counselled concerning the necessity of taking the entire course of medication. A hidden cost here is the extra time required of the provider to provide this counselling.

Clearly, comparative trials of amoxicillin versus azithromycin in different patient populations would

be very useful in determining the best approach to treating chlamydial infections during pregnancy.

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