Sexually transmitted infections (STIs) are a major health problem in many parts of the developing world. STIs cause substantial morbidity and mortality, which disproportionately affect women. Because many of the complications are pregnancy related, adequate diagnosis and effective treatment of STIs in pregnancy are critical. Additionally, there is substantial evidence that the presence of other STIs increases both HIV infectiousness and susceptibility, and a long-term STI control programme is emphasised as one of the cornerstones of HIV prevention.

Striving for optimal performance of the STI programme is essential; in countries where healthcare budgets are limited, the potential for improvement is often larger and can have a substantial effect on the overall burden of disease.

Evaluations of STI programmes are usually limited to an assessment of the proportion of patients with an STI that is correctly diagnosed and to the prescribing of effective drugs. Previous studies have tended not to focus on the fact that patients with an STI must overcome a series of hurdles after their encounter with the healthcare system before they can be considered cured. STI clients who are adequately assessed must obtain prescribed drugs, comply with treatment, and ensure that their partners are treated to avoid reinfection.

Patient compliance with medical advice and drug regimens is an increasingly significant issue in developing countries. The consumption of drugs is on the rise, and drugs represent a substantial share of the total drug use in the country. Despite the large number of prescriptions, treatment success among STI patients in the primary healthcare system remains unknown.

The aim of this article is to draw attention to the consequences of prescribing antibiotics to STI patients in Botswana and to discuss possibilities for improving the cure rates. In a larger research project on STIs among antenatal care (ANC) clients in Botswana, we found that many of the women had a history of STI symptoms in their current pregnancies and had been prescribed the recommended STI treatment. Given the epidemiological data, we present the following research question: Is there a lower prevalence of Chlamydia trachomatis and Neisseria gonorrhoeae among ANC clients who have had drugs against these bacteria prescribed to them in their current pregnancy, compared to ANC clients who have not had these drugs prescribed?

METHOD

Included in this study were 703 ANC clients who visited the primary healthcare clinics in Gaborone, the capital of
Botswana, between October 2000 and February 2001. A proportionate sample of ANC clients was chosen from each of the clinics, based on the ANC patient load during the same period in the previous year. All volunteers gave written, informed consent, and our only exclusion criterion was the use of antibiotics in the 2 weeks before their visit. A structured interview and data from the patient held obstetric record were used to obtain information on sociodemographic factors, past and current pregnancies, and STI symptoms.

When a patient is diagnosed with an STI syndrome during pregnancy, the syndrome and the prescribed drugs are documented in the obstetric record. In pregnant women, STIs are often diagnosed during the mandatory speculum examination at the first ANC visit. A structured interview and data from the patient held obstetric record were used to obtain information on sociodemographic factors, past and current pregnancies, and STI symptoms.

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All patients underwent a genital examination, and clinical signs from external and internal genitalia were recorded. Signs of a sexually transmitted infection were classified into defined syndromes following the national guidelines and were treated accordingly. Cervical swabs were obtained from all women for ligase chain reaction (LCR) amplification technology for the direct, qualitative detection of specific target nucleic acid sequences of *C. trachomatis* and *N. gonorrhoeae*. The swabs were placed in LCx transport media, transported to the laboratory at ambient temperature the same day, and stored at −20°C before batch processing. The LCx assays (Abbott Laboratories, IL, USA) were performed according to the manufacturer’s instructions. A case of *C. trachomatis* or *N. gonorrhoeae* infection was defined as an individual with a positive LCR analysis. DNA amplification testing methods can remain positive up to 3 weeks after treatment. A positive test performed 3 or more weeks after completed treatment should thus be interpreted as true positive, reflecting either treatment failure or re-infection. In this study, rather than assume that every patient began medication the day she received her prescription, we calculated up to 2 weeks to complete the course of medication. Patients who had been prescribed treatment for either of the two infections under study were therefore divided into two groups: (a) patients for whom treatment was prescribed up to 5 weeks earlier and who were still within the period in which a confirmed case of infection could be a false positive, and (b) patients for whom treatment was prescribed 5 or more weeks previous, and for whom a confirmed case was likely to be true positive. Patients who had not been prescribed treatment were used as controls.

The study was approved by the national ethics committees of Botswana and Norway.

**RESULTS**

The median age of the 703 ANC clients was 25 years and the median gestational age 30 weeks (range 8–42); 53 (8%) of the women had a laboratory verified *C. trachomatis* infection and 21 (3%) had laboratory verified *N. gonorrhoeae* infection. Further background characteristics and genital symptoms and signs are described in table 1. Both erythromycin and
Ceftriaxone had been prescribed to 132 of the women earlier in their pregnancies; erythromycin only had been prescribed to 14 women and ceftriaxone only to 10 women. Figure 1 shows the distribution of confirmed cervical infections among women who had and had not been prescribed erythromycin and/or ceftriaxone.

The diagnosis for which the antibiotics were prescribed is shown in table 2. Vaginal discharge syndrome (VDS) was the most common diagnosis, leading to 137 (86%) of 159 erythromycin prescriptions and 130 (85%) of 153 ceftriaxone prescriptions. According to national syndromic management guidelines,11 a woman who complains of abnormal vaginal discharge should, if the condition is confirmed at a speculum examination, be prescribed treatment for vulvovaginal candidiasis, trichomoniasis, bacterial vaginosis, chlamydia, and gonorrhoea. How many of these women actually had chlamydia, gonorrhoea or any of the other infections is not known.

There was no significant difference in the prevalence of chlamydia or gonorrhoea among women with and without clinical signs of vaginal discharge syndrome: 27 (9%) of the 308 women with VDS and 26 (7%) of the 395 women without VDS had chlamydia (Fisher’s exact test 0.31 (two sided)), and 13 (4%) of the 308 women with VDS and eight (2%) of the 395 women without VDS had gonorrhoea (Fisher’s exact test 0.12 (two sided)). Using only clinical signs of abnormal vaginal discharge as a diagnostic tool to identify cervical infections in this study population has a low sensitivity and specificity; VDS has a sensitivity of 0.51 for chlamydia and 0.62 for gonorrhoea and a specificity of 0.57 for both chlamydia and gonorrhoea.

Of the 703 ANC women, 146 (21%) had been prescribed the recommended erythromycin regimen for chlamydia—13 of them twice. The prevalence of chlamydia among women who had and had not been prescribed erythromycin is identical at 8%. Confirmed C trachomatis cases in the different erythromycin prescription groups are shown in table 3; none of these prevalences are significantly different. Of the 116 women who had been prescribed erythromycin 5 or more weeks earlier (median 11 weeks), eight (7%) had chlamydia; and 21 (4%) of the 561 women who had not been prescribed this drug during pregnancy had chlamydia (Fisher’s exact test 1.0 (two sided)). There were no significant differences in age, median gestational week, parity, educational level, marital status, or length of current relationship among the women who had and had not been prescribed erythromycin earlier in pregnancy.

Of the 703 ANC women, 142 (20%) had been prescribed ceftriaxone in their current pregnancy, 11 of them twice. Among these 142 women, none had a positive N gonorrhoeae test result. Among the 110 women who had been prescribed ceftriaxone 5 or more weeks earlier (median 12 weeks), none had gonorrhoea, whereas 21 (4%) of the 561 women who had not been prescribed the drug had gonorrhoea (table 3). The difference in gonorrhoea prevalence between the two groups is significant (Fisher’s exact test = 0.035 (two sided)).

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**Table 1** Background characteristics, genital symptoms and signs, and the prevalence of cervical infections among 703 antenatal care clients in Gaborone, Botswana

| No (%) |  
|--------|---
| **Age groups (years)** |  
| 15–19 | 76 (11)  
| 20–24 | 249 (35)  
| 25–29 | 183 (26)  
| 30–34 | 126 (18)  
| 35–43 | 69 (10)  
| **Education** |  
| Primary school or less | 168 (24)  
| Junior secondary school | 310 (44)  
| Secondary school or higher | 225 (32)  
| **Marital status** |  
| Married | 114 (16)  
| Living with husband | 97 (85)  
| Non-marital steady partner | 572 (81)  
| Living with partner | 256 (45)  
| Single | 17 (2)  
| **Number of pregnancies** |  
| 1st pregnancy | 243 (35)  
| 2nd pregnancy | 208 (30)  
| 3rd pregnancy | 122 (17)  
| 4th+ pregnancy | 130 (18)  
| **Number of antenatal care visits** |  
| 1st visit | 157 (22)  
| 2nd–4th visit | 300 (43)  
| 5th–7th visit | 182 (26)  
| 8th+ visit | 64 (9)  
| **Self reported symptoms of STIs** |  
| Increased vaginal discharge | 119 (17)  
| Itching/soreness | 58 (8)  
| Lower abdominal pain | 53 (8)  
| Genital warts | 16 (2)  
| Genital ulcer | 8 (1)  
| Dysuria | 8 (1)  
| **Clinical signs of STIs** |  
| Vaginal discharge syndrome | 308 (44)  
| Genital warts | 29 (4)  
| Genital ulcer | 5 (1)  
| Cervical infection (chlamydia and/or gonorrhoea) | 67 (10)  
| Chlamydia | 53 (8)  
| Gonorrhoea | 21 (3)  

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differences in the effect of prescribing these two drug injection against N gonorrhoeae pregnancy and that ceftriaxone prescribed as a single dose C trachomatis does not necessarily lead to a cure for prescribing erythromycin orally four times daily in 10 days during pregnancy. We demonstrate that prescribing erythromycin appears to be effective. The differences in the effect of prescribing these two drug regimes are thought provoking.

When the correct drug has been prescribed, patient compliance and treatment of an infected partner are the main factors necessary for the successful treatment of STIs. Research on these issues can be limited by methodological pitfalls, and different research strategies should complement each other. Studies, primarily from developing countries, have measured compliance and partner notification in randomised, controlled trials. Yet these methods are hampered by challenges such as observational bias (patients are likely to perform better in a defined research setting), or there may be a self selection of patients, in that the less conscientious individuals will be lost during the follow up stage.

Epidemiological data have an advantage in evaluating the true effect of STI management from a public health perspective—in this case, illustrating the impact of treating cervical infections among ANC clients in the primary healthcare system in Botswana. A methodological weakness in our study, which is an inherent problem of syndromic management, is the unknown prevalence of infection before the prescription of antibiotics. ANC clients who were and were not prescribed erythromycin earlier in pregnancy demonstrate a similar prevalence of chlamydia. Is there reason to believe that the prevalence of chlamydia among clients who had been prescribed erythromycin was higher before treatment, and was therefore significantly reduced? The answer to this question is mainly dependent on the sensitivity of the clinical signs on which the prescription was based. The majority (85%) of the patients had had erythromycin prescribed to them because of clinical signs of VDS. It is well known that the algorithms currently available for the management of cervical infections are far from ideal. Previous research from Africa reports no or poor association between vaginal discharge and cervical infections. In our data we do not find a significant association between VDS and C trachomatis infection among pregnant women. It is also relevant to note that the women who had and the women who had not had erythromycin prescribed to them earlier in their pregnancies are similar in sociodemographic risk factors, including age—a consistent risk factor for cervicitis. Thus, circumstantial evidence indicates that the prevalence of cervical infection among the patients who had been prescribed erythromycin and/or ceftriaxone was probably the same or slightly higher before treatment.

Lack of efficacy in the prescribed antibiotics is not likely in this study. Erythromycin and ceftriaxone have been shown to be effective against C trachomatis and N gonorrhoeae respectively, and bacterial resistance to these treatment regimens has not yet been found to be of clinical importance. The availability of STI drugs is high in Botswana, even in rural areas, and they are provided to the patients free of charge. Of the 122 women who had had erythromycin and/or

<table>
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<tr>
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<th>Diagnosis leading to prescription of erythromycin and ceftriaxone to 156 antenatal care clients in Gaborone, Botswana, of which 132 clients were prescribed both drugs, 14 clients were prescribed erythromycin only, and 10 ceftriaxone only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reasons for prescribing 500 mg of erythromycin</td>
<td>1 × 4 in 10 days to 146 women, 13 of whom were diagnosed twice (n = 159)</td>
</tr>
<tr>
<td>Vaginal discharge syndrome</td>
<td>137 (86)</td>
</tr>
<tr>
<td>Cervical erosion</td>
<td>18 (11)</td>
</tr>
<tr>
<td>Lower abdominal pain</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Genital ulcer</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

| Reasons for prescribing 250 mg of ceftriaxone intramuscularly, single dose to 142 women of whom 11 were diagnosed twice (n = 153) |
| Vaginal discharge syndrome | 130 (85) |
| Cervical erosion | 17 (11) |
| Lower abdominal pain | 2 (1) |
| Genital ulcer | 3 (2) |
| Syphilis | 1 (1) |

**DISCUSSION**

This retrospective study reviews treatment success among ANC clients who were prescribed drugs for C trachomatis and N gonorrhoeae during pregnancy. We demonstrate that prescribing erythromycin orally four times daily in 10 days does not necessarily lead to a cure for C trachomatis in pregnancy and that ceftriaxone prescribed as a single dose injection against N gonorrhoeae appears to be effective. The differences in the effect of prescribing these two drug regimes are thought provoking.

When the correct drug has been prescribed, patient compliance and treatment of an infected partner are the main factors necessary for the successful treatment of STIs. Research on these issues can be limited by methodological pitfalls, and different research strategies should complement each other. Studies, primarily from developing countries, have measured compliance and partner notification in randomised, controlled trials. Yet these methods are hampered by challenges such as observational bias (patients are likely to perform better in a defined research setting), or there may be a self selection of patients, in that the less conscientious individuals will be lost during the follow up stage.

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<tbody>
<tr>
<td>500 mg erythromycin</td>
<td>1 × 4 in 10 days to 146 women, 13 of whom were diagnosed twice (n = 159)</td>
</tr>
<tr>
<td>C trachomatis infection</td>
<td></td>
</tr>
<tr>
<td>No erythromycin prescribed</td>
<td>42 (8)</td>
</tr>
<tr>
<td>Erythromycin prescribed less than 5 weeks earlier</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Erythromycin prescribed 5 or more weeks earlier</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Total sample</td>
<td>53 (8)</td>
</tr>
</tbody>
</table>

| Caeftriaxone 250 mg im in a single dose | N gonorrhoea infection |
| No caeftriaxone prescribed | 21 (4) |
| Caeftriaxone prescribed less than 5 weeks earlier | 0 |
| Caeftriaxone prescribed 5 or more weeks earlier | 0 |
| Total sample | 21 |

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ceftiraxone prescribed to them 5 or more weeks before this study, 104 (85%) had had both drugs prescribed. No substantial crossover effect between the two drugs is likely, however. Neither drug regimen is satisfactory for treatment of the other microbe,21 and we found no significant reduction of gonorrhoea among patients who were prescribed erythromycin and no significant reduction in chlamydia among patients who were prescribed ceftriaxone.

Re-infection
Could the treatment failure of erythromycin be due to re-infection or to a newly acquired infection? Chlamydia and gonorrhoea can cause urethral discharge in men, and men with this symptom and partners to women with VDS are usually treated with both doxycycline and ceftriaxone. Among the ANC clients in this study with an N gonorrhoeae infection who were prescribed ceftriaxone, all were treated successfully and had not been re-infected by their partners at the time of our study. Two factors can possibly lead to a lower impact of re-infection with N gonorrhoeae than with C trachomatis in this population. We cannot ignore the fact that the level of healthcare seeking among partners with gonorrhoea (which causes symptoms among men more often than does chlamydia) is likely to be somewhat higher. It is also possible that treatment success with the single dose therapy for gonorrhoea is higher among partners than is the doxycycline regimen for chlamydia.

Theoretically, all women treated for chlamydia could have been re-infected or acquired a new infection after being cured. However, it would have required a substantial failure in the notification and treatment of the partners of ANC clients with C trachomatis and complete success in notifying and treating partners of the women with an N gonorrhoeae infection—a highly unlikely state of affairs. Sexual abstinence in the gonorrhoea group could explain their lack of re-infection and multiple partners in the chlamydia group could have caused new infections, but there is no reason to believe that that would have been the case. Women in both groups reported one sexual partner the last year and it seems safe to assume that these two groups should not differ systematically in their sexual behaviour. These arguments lead to the conclusion that re-infections or new infections can not be a major cause of the documented failure to treat C trachomatis. One is left with the impression that patient compliance is a more important variable.

Patient compliance
Although evidence from developing countries is limited, a substantial level of non-adherence to antibiotic prescriptions in most cultures is well known and reviews of studies from developed countries suggest that at least 30% of patients fail to follow medical advice on drug use.20 Of the many variables involved in non-adherence, non-modifiable factors include characteristics of the patient, practitioner, or illness; whereas potentially modifiable factors relate to aspects of the interaction between patient and healthcare provider and aspects of the drug regimen. The complexity of the regimen (frequency of administration, number of tablets required daily, and length of treatment) is closely related to adherence.21 The number of patients who do not comply with prescribed courses of antibiotics may be increased in asymptomatic STI clients, and the occurrence of adverse effects is also associated with non-compliance.21

As in most developing countries, ANC clients in Botswana with STI symptoms are prescribed a multiple drug regimen that requires many tablets to be administered correctly, which in itself may reduce compliance. The erythromycin regimen is complex in itself, the medication is frequently followed by gastrointestinal side effects, and the patient’s complaint is not severe. We suspect that low compliance is a central factor in explaining why the prescribing of erythromycin orally four times daily in 10 days does not necessarily lead to a cure for C trachomatis in pregnancy.

Improving cure rates
According to national guidelines in Botswana, all STI patients should be counselled on patient based partner referral and should receive contact cards with information to give to their partners. However, referred partners to symptomatic STI patients comprise less than 10% of all registered STI outpatients,20 suggesting that there is room for improvement in the partner notification system. Unfortunately, few studies on this issue have been undertaken in resource poor countries where it is essential that resources be used effectively and efficiently, and the cultural contexts are different.21 The relatively high levels of overdiagnosis of STIs in syndromic management, especially in women, may not, in fact, provide an appropriate basis for recommending the management of partners, as we may not be sure that the individual is truly infected.24 Thus, improving partner notification in women with VDS is a complicated issue. A more obvious and simple strategy to improve C trachomatis cure rates within the national control programmes is the use of a single, supervised dose of antibiotics.

Several drugs, typically used in combination, can satisfactorily cure cervical infections. If poor compliance is suspected, as is the case with the ANC clients in Gaborone who are treated with erythromycin for C trachomatis infections, directly observed single dose therapy should be considered.25 Gonorrhoea has been treated in this manner since the beginning of the antibiotic era; and with the development and licensing of azithromycin, chlamydia can also be effectively treated with single dose therapy.26 The oral administration of 1 g of azithromycin has a similar or higher efficacy and similar or fewer side effects than all the alternative week long regimens,12 27 and has become the drug of choice in most of the developed world. Although azithromycin is still not officially licensed for the treatment of chlamydia in pregnancy, clinical experience and research data suggest that azithromycin is effective and safe for the fetus.13 28 and the drug is listed as an alternative regimen for pregnant women in the Centres for Disease Control STD treatment guidelines.25 Compared to azithromycin, erythromycin has a significantly higher level of gastrointestinal side effects, which frequently discourage patients from complying with the regimen and thereby reduces the cure rate.29 29

A comparative study on STI drugs from 15 countries in Africa and Asia concludes that azithromycin is not routinely used for chlamydia in developing countries.30 Single dose therapies were used to treat N gonorrhoeae in 12 out of 15 countries, but week long regimens were used in all 15 countries to treat C trachomatis. Efficacy, tolerance, compliance, and cost are factors to consider when preparing guidelines for antibiotic treatment of chlamydial infection. An important obstacle to single dose therapy in countries where resources are limited is the higher drug acquisition cost for azithromycin compared to doxycycline. The erythromycin regimen is more expensive than azithromycin, and in pregnant women, azithromycin could be recommended.31 When it comes to other STI patients, economic analysis clearly favours single dose therapy when the indirect costs of treatment failures are included.28

It is also clear that an investment of additional time is necessary during consultation in order to provide patient education and counselling on compliance, partner notification, and safe sex. Female STI patients in Botswana are managed in an average of 5.4 minutes.22
CONCLUSION

When assessing the performance and cure rates achieved by STI programmes, it is necessary to focus on the consequences of the STI patient’s diagnosis and treatment prescription. Low compliance with recommended drug regimens and lack of partner notification and treatment are the main obstacles that hinder a cure. In this study, many ANC clients in Botswana are successfully treated on the spot for N. gonorrhoeae with an intramuscular injection with ceftriaxone, whereas many clients who are prescribed one tablet of erythromycin four times daily for 10 days are not cured of C. trachomatis. We argue that the complexity of the erythromycin regimen most probably is the main cause of the low treatment effect.

Improving patient compliance, but also facilitating partner notification, and promoting sexual abstinence until the patient and partner are treated can be effective and cost effective ways to improve treatment with STI drugs. The use of directly observed single dose therapy for the treatment of chlamydia should be considered if low compliance to more complex treatment regimens is likely.

CONTRIBUTORS

MRo contributed to the study design, was responsible for data collection and data analysis, and was the primary author of the manuscript. MRA contributed to the study design, and to formal and organisational aspects of the study. JS and PH supervised the study; all co-authors contributed to the drafting of the article and approved the final manuscript.
Chlamydia and gonorrhoea in pregnancy: effectiveness of diagnosis and treatment in Botswana

M Romoren, M Rahman, J Sundby and P Hjortdahl

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