SYNDROMIC MANAGEMENT

Lack of effectiveness of syndromic management in targeting vaginal infections in pregnancy in Entebbe, Uganda

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Objectives: To measure the prevalence of reproductive tract infections (RTIs) during pregnancy in Entebbe, Uganda, and to evaluate the current syndromic diagnosis and management approach in effectively targeting infections, such as bacterial vaginosis (BV) and trichomoniasis, that are associated with low birth weight and prematurity among newborns.

Methods: We enrolled 250 antenatal clinic attenders. Vaginal swabs and diagnostic tests were performed for BV, *Trichomonas vaginalis* (TV), candida, *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and for HIV-1 and active (TPHA+/RPR+) syphilis infection. Same day treatment was offered for symptoms according to syndromic management guidelines. The treatment actually provided by healthcare workers was documented. Sensitivity, specificity, positive and negative predictive values were used to assess the effectiveness of syndromic management guidelines and practice.

Results: The prevalence of infections were: BV 47.7%, TV 17.3%, candida 60.6%, gonorrhoea 4.3%, chlamydia 5.9%, syphilis 1.6%, and HIV 13.1%. In total, 39.7% of women with BV and 30.2% of those with TV were asymptomatic. The sensitivity of syndromic management as applied by health workers in targeting BV and TV was 50.0% and 66.7%, respectively. This would have increased to 60.3% (BV) and 69.8% (TV) had the algorithm been followed exactly.

Conclusions: The prevalence of BV and TV seen in this and other African populations is high. High rates of asymptomatic infection and a tendency of healthcare workers to deviate from management guidelines by following their own personal clinical judgment imply that many vaginal infections remain untreated. Alternative strategies, such as presumptive treatment of BV and TV in pregnancy, should be considered.

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A high prevalence of vaginal infections such as bacterial vaginosis (BV) and *Trichomonas vaginalis* (TV) has been observed among both pregnant,[1–4] and non-pregnant women,[5–7] in Africa. Both BV and TV are associated with a number of adverse pregnancy outcomes including preterm rupture of membranes, preterm delivery, and low birthweight infants.[8–10] Prematurity and low birth weight are among the leading causes of perinatal morbidity and mortality in developing countries. Previous studies from east Africa have reported a high prevalence of BV and TV; a study among a rural Ugandan cohort in Rakai reported prevalences of 51% and 24% for these infections, respectively.[5] Antenatal treatment of vaginal infections has been shown in some studies to be effective in reducing the incidence of adverse pregnancy outcomes, particularly in women who are at high risk of preterm delivery.[1 11–14] Recent studies suggest that BV may increase the risk of acquisition of HIV infection.[15–17] Effectively treating women with BV may therefore reduce susceptibility to HIV and, during pregnancy, may have an effect on mother to child transmission of HIV.[17–19]

In resource poor, primary care settings, diagnostic facilities to aid the effective management of reproductive tract infections (RTIs) may not be available, and so algorithms based on signs and symptoms of infection are relied upon. The World Health Organization recommends that guidelines are adapted according to local factors such as the prevalence of disease and microbial resistance patterns.[20] In addition, to reflect the unique physiological changes that occur during pregnancy which result in an increased likelihood of yeast infection, WHO algorithms have been adapted for use during this time.[21] Accordingly, in an area locally known to have a low prevalence of cervical infections, all pregnant women reporting vaginal discharge and/or vaginal itch are treated in the first instance for BV and yeast infection. In Uganda, local syndromic management guidelines reflect this and recommend treatment in the first instance with a combination of single dose (2 g) oral metronidazole and clotrimazole pessaries.[22] Although metronidazole is also effective in treating trichomoniasis in pregnancy, partners are not treated as first line, only later, if symptoms persist.[22]

The management of RTIs is complicated not only by the diversity of pathogens involved but also by the fact that symptoms of infection are commonly mild or absent. Among the rural cohort in Rakai, 80% of women with BV or TV were genuinely asymptomatic.[5] On the other hand, vaginal discharge is so highly prevalent in some populations that women may regard it as a normal feature of sexual maturity and therefore do not seek treatment although they may be genuinely infected.[23 24] The effectiveness of these algorithms may be further compromised by the tendency of trained healthcare workers to rely on their own clinical judgment, based perhaps on individual risk assessment or examination findings, in interpreting and applying these guidelines.[8] In addition, spontaneous self reporting of vaginal discharge rather than probing for this symptom is associated with a higher specificity in the detection of infections.[25] Lastly, vaginal discharge is often reported in the absence of infection,[26] particularly by women on contraceptive medication or during pregnancy. Within this climate can we

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Abbreviations: BV, bacterial vaginosis; PCR, polymerase chain reaction; RPR, rapid plasma reagin; RR, relative risk; RTIs, reproductive tract infections; TPHA, *Treponema pallidum* haemagglutination assay; TV, *Trichomonas vaginalis*; UVRI, Uganda Virus Research Institute; VDS, vaginal discharge syndrome

therefore expect syndromic management algorithms to target vaginal infections in pregnancy effectively?

This study aimed to examine the prevalence of RTI among women attending for antenatal care in a semiurban community in central Uganda. In addition, it aimed to evaluate the effectiveness of locally adapted syndromic management guidelines[22] in the correct detection and treatment of vaginal infections such as BV and TV.

METHODS

This study was conducted among women attending for antenatal care at a district hospital in Entebbe, Uganda. The study was reviewed and approved by the ethics committees of the London School of Hygiene and Tropical Medicine and the Uganda Virus Research Institute and by the Uganda National Council for Science and Technology.

All pregnant women attending for their booking visit were eligible to enrol. The greatest limitation on the rate of recruitment was the availability of study staff to counsel antenatal attenders regarding the study and so at busy clinic times eligible women were selected to receive counselling according to convenience. After obtaining written informed consent, a standardised questionnaire was completed by one of four clinic midwives experienced in research techniques, who gathered information on obstetric history and treatments taken during this pregnancy. Women were asked if they had experienced any abnormal vaginal discharge or genital itch within the past 2 weeks.

Following routine obstetric examination, the midwife took four blind high vaginal swabs by inserting two swabs deeply into the vagina and gently rotating them for 5 seconds, this being repeated once. The first swab was rolled on a glass slide, fixed with ethanol, and Gram stained for the diagnosis of BV according to the morphological scoring system described by Nugent *et al*.[27] A score of 7–10 was used to define a diagnosis of bacterial vaginosis and a score of 4–6 that of intermediate flora. Scores of 3 or less were defined as consistent with normal vaginal flora. Five per cent of slides were re-evaluated by an external independent expert slide reader and were consistently within a Nugent score of plus or minus 1 with none requiring re-classification. The second swab was inoculated into a culture media kit for *Trichomonas vaginalis* (InPouch, BioMed Diagnostics, San Jose, CA, USA) and was incubated at 37°C for up to 5 days and examined by light microscopy daily for the presence of motile trichomonads. The third swab was taken using the Roche Amplicor collection kit (Roche Diagnostics, Branchburg, NJ, USA) for the detection of *Neisseria gonorrhoeae* and *Chlamydia trachomatis*

by polymerase chain reaction (PCR); the fourth swab was inoculated onto blood agar, MacKonkey agar, anaerobic blood agar, and Sabauraud agar (Oxoid, Basingstoke, UK) for aerobic, anaerobic, and candidal culture. All microbiology investigations were performed at the MRC/UVRI microbiology laboratory and were used as gold standard for the evaluation of the syndromic diagnosis of RTIs. Quality assurance at the laboratory is maintained through participation in a scheme of the American College of Pathologists with consistently good results.

A venous sample was taken from participants for syphilis serology using a specific treponemal antibody test (*Treponema pallidum* haemagglutination assay, TPHA) and rapid plasma reagin (RPR) test (both Biotec Laboratories, Ipswich Suffolk, UK). RPR titres were determined where RPR was found to be positive. A diagnosis of active syphilis was defined as serology positive for both TPHA and RPR for any titre. Affected women were treated with benzathin penicillin (2.4 MU intramuscular single dose) weekly for 3 weeks. Participants were offered voluntary counselling and testing for HIV as part of the hospital prevention of mother to child transmission programme. HIV testing was performed using rapid antigen tests; an initial screening test was performed (Determine, Abbott Laboratories, Abbott Park, IL, USA) followed by a confirmatory test in those found to be HIV positive (UniGold, Trinity Biotech Plc, Ireland). In the event of discordant results a third test (InstantScreen, Gaifar GmbH, Biotech Campus Potsdam, Germany) was performed to confirm HIV status.

Clinical study staff were trained in the syndromic management of RTIs in line with local guidelines (Ugandan Ministry of Health[24]), which do not include risk score assessment or cervical examination (fig 1). According to these guidelines women of any gestation, complaining of vaginal discharge and/or itch (defined here as vaginal discharge syndrome (VDS)), are treated in the first instance with single dose (2 g) oral metronidazole and clotrimazole pessaries. Partners of affected women are not offered treatment at this stage. Women in whom symptoms persist are treated with antibiotics to cover cervical infections (erythromycin 500 mg four times daily for 7 days and cotrimoxazole 2.4 mg twice daily for 3 days) and are counselled with regard to partner notification and treatment. Women presenting with signs and symptoms suggestive of an upper genital tract infection were to be referred for further management and excluded from the study: however no such women presented during the study. All participants were evaluated and treated for infections on the day of screening. Participants found later, on laboratory testing, to have an untreated infection were given specific treatment at the next follow up visit and where appropriate were counselled with regard to partner notification and treatment.

The principal outcome in this study was the presence of BV and/or TV. A sample size of 250 women was required to estimate the prevalence of these infections with a 95% confidence interval of plus or minus 5% if the prevalence of each was 20%. Data were entered using Excel (Microsoft) and analysed using Stata software (version 8: StataCorp). Prevalence of vaginal infections were calculated and compared using Fisher's exact test, χ^2 and χ^2 for trend as appropriate. Sensitivity, specificity, and positive and negative predictive values were used to assess the effectiveness of syndromic management guidelines and practice.

RESULTS

A total of 250 consecutive pregnant women were enrolled over a 5 week period commencing 1 March 2004 from a total of 594 women attending the antenatal clinic. Participants were between the ages of 15 years and 40 years
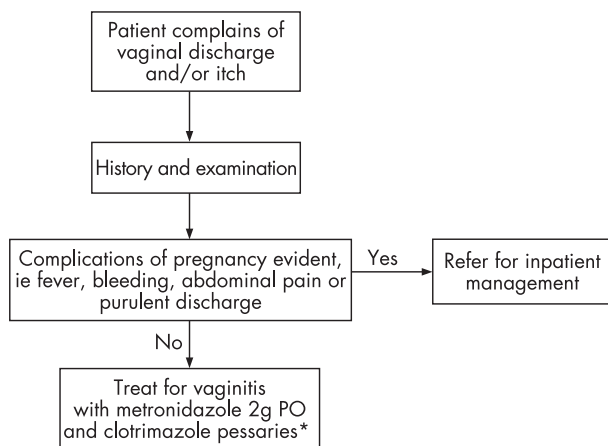

Figure 1 Algorithm for the management of vaginal discharge in pregnancy. *Partners are not referred for treatment at this stage.

Table 1 Prevalence of RTIs and HIV

Infection	No	%	95% CI
Reproductive tract infections			
Bacterial vaginosis*	117/247	47.7	41.0 to 53.8
Intermediate flora*	35/247	14.2	10.1 to 19.2
T vaginalis	43/249	17.3	12.8 to 22.6
Candida sp	151/249	60.6	54.3 to 66.8
N gonorrhoeae†‡	10/233	4.3	2.1 to 7.7
C trachomatis†	14/236	5.9	3.3 to 9.7
Any aerobic organism	60/249	24.1	18.9 to 29.9
Coliform species	38/249	15.3	11.0 to 20.3
Group B streptococcus	4/249	1.6	0.4 to 4.1
Streptococcal species	20/249	8.0	5.0 to 12.1
Staphylococcus aureus	5/249	2.0	0.7 to 4.6
Serology			
HIV +	27/206	13.1	8.8 to 18.5
Syphilis (TPHA +/RPR +)	4/245	1.6	0.4 to 4.1

*Insufficient material on slides to test for the presence of BV in two participants.
†Inhibitors were present in the PCR specimen for 13 participants.
‡Equivocal PCR result for three participants.

(median 22 years). Gestation varied between 8 weeks and 39 weeks (median 26 weeks) and parity between 0 and 9 (median 1). The most commonly reported symptoms suggestive of a current RTI were abnormal vaginal discharge (44.3% (108/244)) and vaginal itching (43.0% (107/249)) with 54.9% (134/244) of women reporting any of these symptoms. Only two women (2/245) reported using an antibiotic that may be effective in treating BV or TV during this pregnancy.

Samples for laboratory diagnosis of vaginal infections were obtained for 249 participants. All study participants received voluntary counselling and testing for HIV and 206 of these (82%) accepted HIV testing. Serum samples for syphilis serology were collected from 245 women. The prevalence of vaginal infections was high (table 1). Eight per cent of participants were positive for at least one cervical STI.

Samples from a quarter of women isolated an aerobic organism that may be associated with early neonatal sepsis although the prevalence of group B streptococcus was low. Only one of the four women found to be positive on TPHA and RPR laboratory testing exhibited an RPR titre of greater than one in four.

No significant differences were seen in the prevalence of BV by age group or parity. The prevalence of BV decreased significantly ($p = 0.038$, χ^2 for trend) with gestation (first trimester 75.0% (6/8), second trimester 50.0% (70/140), third trimester 39.8% (35/88). A positive association was seen between the prevalence of HIV and all RTIs, but this was only statistically significant for BV (HIV prevalence, 18.5% in women with BV versus 8.1% in women without, relative risk (RR) 2.28 (95% confidence interval (CI) 1.07 to 4.87), $p = 0.035$) and TV (HIV prevalence 25.0% v 10.4%, RR 2.40 (95% CI 1.14 to 5.05), $p = 0.038$).

A high proportion of women reported no symptoms of vaginitis despite testing positive for a vaginal infection (table 2).

Syndromic management guidelines apply only to women with self reported vaginal symptoms (fig 1). To evaluate the accuracy to which trained clinical study staff adhered to the guidelines a distinction was made between the symptoms participants reported and the syndromic management that they received. Table 3 shows the sensitivities, specificities, and predictive values for self reported vaginal symptoms and for the treatment actually provided by health worker for women positive for BV and TV respectively.

DISCUSSION

The prevalence of BV and TV was found to be high among antenatal clinic attenders in Entebbe and this is consistent with findings of other studies from the region.[1] [5] [7] It is possible that women who thought that they were at greater risk of a STI may have been more likely to attend the hospital clinic or participate in the study, leading to an overestimation of the true prevalence of RTIs in our population. We compared the HIV prevalence observed in our study with that from all women attending the antenatal clinic during the study period, which was slightly lower (13.1% among study participants versus 11.4% among all attenders, unpublished data). This difference, however, was not statistically significant, and we conclude that there was no important bias in the study's findings. A significant decrease in the prevalence of BV was seen with increasing gestation. Natural alterations in the vaginal microbial ecosystem known to occur during pregnancy may account for this, in particular increasing concentrations of lactobacilli seen at advancing gestation may provide improved protection against potentially pathogenic bacteria.[28]

Despite the high rates of symptom reporting, 30–40% of laboratory positive infections were asymptomatic. It is possible that symptomatic women may be over-represented since those suffering from troublesome genital symptoms may be more inclined to attend antenatal clinic or to

Table 2 Symptoms of vaginal discharge and/or itch in participants positive for a vaginal infection

	Asymptomatic	Symptomatic
Infection	No (%)	No (%)
Bacterial vaginosis*	46/116 (39.7)	70/116 (60.3)
Intermediate flora	11/35 (31.4)	24/35 (68.6)
T vaginalis	13/43 (30.2)	30/43 (69.8)
Candida sp	58/151 (38.4)	93/151 (61.6)

*Information on symptoms unavailable for one participant.

Table 3 Diagnostic statistics for syndromic management of BV and TV

	BV			TV		
	Numerator/denominator	%	95% CI	Numerator/denominator	%	95% CI
Vaginal discharge syndrome according to symptoms recorded*						
Sensitivity	70/116‡	60.3	50.8 to 69.3	30/43§	69.8	53.9 to 82.8
Specificity	63/128‡	49.2	40.3 to 58.2	96/203§	47.3	40.3 to 54.4
Positive predictive value	70/135‡	51.8	43.1 to 60.5	30/137§	21.9	15.3 to 29.8
Negative predictive value	63/109‡	57.8	48.0 to 67.2	96/109§	88.1	80.5 to 93.5
Syndromic diagnosis of VDS made (and treatment provided) by health worker†						
Sensitivity	58/116¶	50.0	40.6 to 59.4	28/42**	66.7	50.4 to 80.4
Specificity	68/127¶	53.5	44.5 to 62.4	113/203**	55.7	48.5 to 62.6
Positive predictive value	58/117¶	49.6	40.2 to 59.0	28/118**	23.7	16.4 to 32.4
Negative predictive value	68/126¶	54.0	44.9 to 62.9	113/127**	89.0	82.2 to 93.8

*Self reported symptoms of vaginal discharge and/or itch by women.
†Actual treatment administered.
‡3 women absent data on symptoms, (n=244).
§3 women with absent data on symptoms, (n=246).
¶4 women absent data on treatment, (n=243).
**4 women absent data on treatment, (n=245).

participate in the study. However, since women within this community generally find it easy to access a peripheral community clinic for this purpose it is likely that this had minimal effect on our results.

A positive association was seen between HIV status and a diagnosis of BV and TV. Women testing positive for a vaginal infection exhibited a twofold risk of HIV infection when compared to those without. Higher rates of sexual risk taking common to the acquisition of HIV and other STIs may in part account for this association; but there may also be a genuine biological link. While the direction of causality in the association between BV and HIV cannot be established from our study, other studies suggest that BV may represent an increased risk of HIV acquisition.[15 16] The association between TV and HIV infection has also been described by others.[29 30]

In our study only half of women with BV and two thirds of those with TV were offered appropriate treatment for their infection when managed with local syndromic management guidelines. In addition, TV was ineffectively targeted because partners do not receive treatment in the first instance according to the Ugandan guidelines. The clinic staff had considerable experience in the antenatal clinic setting, and were trained in and familiar with the use of syndromic management guidelines. Communication with study staff revealed that case management at an individual level may be

influenced by their own clinical judgment of signs of infection found on examination in addition to reported symptoms. The modification of guidelines based on individual clinical judgment clearly undermined the effectiveness of guidelines in targeting BV and TV and this highlights the importance of accurate use of syndromic algorithms.

The high prevalence of vaginal infections seen in our study is likely to reflect the situation in similar communities across sub-Saharan Africa and suggests they may be having a significant impact on the incidence of adverse pregnancy outcomes. As shown, many infections remain untreated for different reasons. While there is some evidence that effective treatment of vaginal infections during pregnancy may prevent adverse birth outcomes, reliance on syndromic management is unlikely to achieve this goal. Alternative and innovative solutions, including presumptive treatment strategies should be considered if we are to ensure that effective treatment is delivered to all affected women.

CONTRIBUTORS
CT contributed to the design of the study, data analysis and interpretation and drafted the manuscript; HM and MO contributed to acquisition of study data and to care of the participants; LM performed data analysis and interpretation and assisted in the drafting of the manuscript; KN was the technician responsible for processing microbiological samples; PH supervised the laboratory aspects of the study and contributed to the study design;. MM contributed to study design and organisation; DM, HG, AME contributed to the study design, organisation, interpretation of the data and the writing of the report. All authors have reviewed and approved the final version of the paper.

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Key messages

- The high prevalence of vaginal infections, such as bacterial vaginosis and *Trichomonas vaginalis*, seen among antenatal attenders in Africa suggests that they could have a significant impact on the incidence of adverse pregnancy outcomes
- As a result of high rates of asymptomatic infection and the tendency of healthcare workers to deviate from syndromic case management guidelines and rather follow their personal clinical judgment, many vaginal infections remain untreated
- Alternative interventions, such as presumptive treatment, should be considered to target vaginal infections during pregnancy in areas where these infections are highly prevalent. Studies are required to evaluate the effectiveness of such interventions

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