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REVIEW

Bacterial vaginosis: a public health review

Introduction

In the UK bacterial vaginosis is one the conditions most commonly associated with an abnormal vaginal discharge in reproductive age women[1]. Bacterial vaginosis is a polymicrobial syndrome in which the normal vaginal lactobacilli, particularly those producing hydrogen peroxide, are replaced by a variety of anaerobic bacteria and mycoplasmas. Common agents of bacterial vaginosis include *Gardnerella vaginalis, Mobiluncus, Bacteroides* spp. and *Mycoplasma hominis*[2–4]. The wide range of possible aetiologies is reflected in the variation in symptoms associated with bacterial vaginosis: these include grey, homogenous vaginal discharge; odorous discharge (fishy smell); increased discharge without an inflammatory response; yellow discharge; abdominal pain; intermenstrual bleeding; menorrhagia or prolonged menses. Up to 50% of women are asymptomatic[5]. This variation is captured by the clinical definition of bacterial vaginosis requiring three of the four composite criteria to be met[6]

1. Thin, homogenous, uniformly adherent, white discharge.
2. Vaginal pH $>$ 4.5.
3. Fishy odour on addition of 10% KOH.
4. 20% clue cells (epithelial cell margins obscured by bacteria) on microscopic examination of vaginal smear.

The aetiology of bacterial vaginosis has been under debate. It is uncertain whether bacterial vaginosis should be classified as a sexually transmitted condition or is an example of abnormal microbial colonisation[7–11]. Until this is resolved preventive action against bacterial vaginosis is difficult to initiate. The public health importance of bacterial vaginosis remains ambiguous, as it is uncertain whether bacterial vaginosis is the cause of substantial reproductive morbidity, particularly preterm birth and upper genital tract infection, or is simply an offensive vaginal discharge[12–15].

This narrative review aims to critically assess current knowledge of the epidemiology of bacterial vaginosis and its sequelae. The review focuses on the public health importance of bacterial vaginosis, whether or not it fits the characteristics of being a sexually transmitted infection and the potential gains to be made from its control and prevention.

Aetiology

The loss of endogenous vaginal lactobacilli is important in the acquisition of the bacterial vaginosis. A cohort study of 182 women attending a genitourinary medicine clinic in the United States found that the acquisition of bacterial vaginosis was independently associated with a specific lack of vaginal H_2O_2-producing lactobacilli (HR 4.0, $P < 0.001$). This relationship was not seen for women with candidiasis and trichomoniasis[16]. Close analysis of the H_2O_2-producing lactobacilli has shown them to be capable of reacidifying the vagina following coital vaginal neutralisation by male ejaculate[17]. During bacterial vaginosis there is a loss of vaginal acidity (pH $>$ 4.5) that correlates with the loss of these lactobacilli. The question remains of what stimulates the lactobacillus loss.

The development of bacterial vaginosis may centre on hormonal changes. A new episode of bacterial vaginosis often occurs after menstruation when oestradiol levels increase[18,19]. Models using the mice have shown that increased levels of oestradiol, characteristic of pregnancy, are associated with increased levels of genital colonisation by mycoplasmas[20].

Once infected there may be synergistic relationships between the acquired organisms. A study of 633 women attending a genitourinary medicine clinic showed that, after adjusting for the presence or absence of bacterial vaginosis, women with *Mobiluncus* were more likely to harbour *G. vaginalis* (OR 2.9, 95% CI 1.4-6.0) and *M. hominis* (OR3.7, 95% CI 2.0-7.0)[3]. The question of whether these microbes cause the syndrome or are a consequence of it remains.

Critique of included studies

The studies reviewed were identified through a search of English language publications since 1984 on the Medline and Cochrane databases using the key words *bacterial vaginosis, anaerobic vaginosis* and *vaginitis.* The review concentrates on several broad categories:

1. prevalence of infection and factors associated with infection;
2. associated morbidity and complications (sequelae);
3. intervention strategies.

There was only one population based study from rural

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Uganda, which might, due to inter-country differences, make the findings difficult to apply elsewhere. Most other studies were based in specialist clinic settings, such as genitourinary medicine clinic or antenatal clinics, reducing their generalisability.

The wide range of symptoms displayed in cases of bacterial vaginosis and the high proportion of asymptomatic infections makes it a difficult syndrome to diagnose and one whose epidemiology is therefore difficult to describe. Such problems have led to the use of a broad clinical definition with the composite criteria, but these have poor reproducibility. There has been a move towards the use of Gram staining of vaginal secretions that is generally althought to be highly sensitive and specific[2,12,21,22]. However, the cost and need for expert microscopists means that diagnosis by Gram staining has not been adopted universally, although it was used in the UK studies reviewed.

Studies investigating morbidity and complications associated with bacterial vaginosis were mostly cross sectional, apart from those considering preterm birth and two HIV-related studies. While this does not limit the validity of the study findings, it makes it impossible to infer a causal relationship between bacterial vaginosis and the relevant outcome. Also many sample sizes were small, reflecting the relative rarity of the complications studied, but limiting their power to detect or reject any associations and their representativeness.

The intervention studies concentrated on preventing preterm birth through the treatment of bacterial vaginosis during pregnancy. The evidence was strengthened through a meta-analysis to overcome the problem of small numbers in certain trials and some dubious methods of randomisation (randomised according to risk of preterm birth rather than bacterial vaginosis status).

Prevalence of bacterial vaginosis

Surveillance of bacterial vaginosis in the UK is restricted to cases diagnosed through genitourinary medicine clinics. In 1998 there were 51,172 cases of bacterial vaginosis reported by such clinics accounting for 18.4% of all diagnoses in females in that setting[23]. This is an under-estimate of the true burden of disease given the high proportion of asymptomatic cases. Prevalence estimates cannot be made, as the clinic population denominators are unknown.

The sole population-based prevalence survey of bacterial vaginosis took place in rural Ugandan villages and reported a prevalence of over 50%[24,25]. While that may be typical of rural Africa it is hard to apply in other settings as the availability of basic hygiene facilities in bacterial vaginosis may be important[25]. The most important predisposing factor for bacterial vaginosis with regard to genital hygiene is douching. African women practice douching more often than women in the UK reinforcing further the inter-country differences[26,27].

Clinic-based prevalence studies employing the systematic screening of patients dominate the literature. Prevalences of between 4.9% and 36% have been reported from European and American studies (Table 1). Higher prevalences have consistently been reported among women attending genitourinary medicine clinic and those requesting termination of pregnancies compared with antenatal and general health clinics. Both genitourinary medicine and termination of pregnancies populations are generally considered to be at a higher risk for the acquisition of a sexually transmitted infection.

One American study from a sexually transmitted disease clinic reported a prevalence of only 11.3%, but it was carried out in the 1970s when awareness differed from today[7]. Contrasting prevalence figures from Swedish health centre studies (10% and 34%) may reflect the method of diagnosis. The lower prevalence was recorded through diagnosis using only clue cells which is known to be a less sensitive method[4,8].

All but one of the reported studies described a prevalence of over 10% indicating that there is a potentially large reservoir of undiagnosed infection in the population. Lack of awareness and confusion arising from an ill-defined case definition may leave many cases undiagnosed unless the patient is seen in a specialised clinical setting.

The first UK prevalence study of asymptomatic women in general practice has just been published. Two hundred and eighty-seven women attending three general practices in Bedfordshire for a routine cervical smear agreed to participate. Nine percent were found to have bacterial vaginosis on gram stain examinations of upper vaginal secretions emphasising the substantial level of infection in the general population[28].

Risk factors

If the acquisition of infection is linked to specific activities, groups participating in those activities will be at a higher risk of contracting the infection. The identification of those groups can allow targeted prevention initiatives to be designed and implemented.

Smoking

Smoking has been consistently associated with bacterial vaginosis and sexually transmitted diseases in UK and Swedish studies[15,29,30]. The results from an antenatal population in London gave a percentage population attributable risk of 8.5% for current smokers against former and non-smokers[15]. However, results from a pregnant population may be of limited generalisability. Smoking may suppress the immune system facilitating infection, but may simply reflect poor health seeking behaviour. No studies have

Table 1. Prevalence of bacterial vaginosis diagnosed using clinical criteria or gram staining. GUM = genitourinary medicine clinic. TOP = termination of pregnancy clinic.

	Country	Prevalence (%)	Diagnostic method	Age range of participants	Symp/asymptomatic infection	Reference
Population-based	Uganda	50.9 (5914/11618)	Clinical criteria	15-59	Symptomatic	Wawer *et al*., 1999[24]
TOP clinic	UK	28 (112/401)	Gram stain, pH > 4.5, KOH test	19-28	Both	Blackwell AL *et al*., 1993[94]
GUM clinic	Sweden	26 (553/2128)	Clinical criteria	14-50	Both	Moi H *et al*., 1990[14]
	Sweden	28 (164/455)	Clinical criteria	16-51	Both	Hallen A *et al*., 1987[95]
	US	11.3 (4613/40821)	Clinical criteria	16-30	Both	MMWR, 1979[7]
	US	33 (210/640)	Clinical criteria	16-50	Both	Eshenbach DA *et al*., 1988[12]
Health clinic	Sweden	34 (34/101)	Clinical criteria	-	Symptomatic	Holst E *et al*., 1987[4]
	Sweden	10 (617/6150)	Clue cells present	30-60	Asymptomatic	Larsson PG *et al*., 1991[8]
Antenatal clinic	UK	12.2. (87/706)	Gram stain	Median age 27	Asymptomatic	Hay PE *et al*., 1994[15]
	Italy	4.9 (70/1441)	Clinical criteria	16-49	Asymptomatic	Cristano S *et al*., 1996 [96]

investigated the association between poor health care seeking behaviour and the incidence of bacterial vaginosis. Smoking could be a marker for sexual behaviour as significantly more of the UK population with more than five lifetime sexual partners are smokers than non-smokers[29,31]. However, that relationship could be confounded by age or by trends in partner change[29].

Racial origin

In both the UK and the United States, black ethnic groups have the highest prevalence of bacterial vaginosis[15,32]. These groups also report higher rates of gonorrhoea and genital chlamydial infection than members of white ethnic groups[33,34]. Vaginal douching is more commonly practised by African American women in the United States and African Caribbean women in the UK than among women from white ethnic groups[35,36]. Douching has been independently associated with acquiring bacterial vaginosis (HR 2.1 95% CI 1.0-4.3)[16]. However, a recent study in inner London hospitals found that after adjustment for genital douching black race was no longer significantly associated with bacterial vaginosis [27]. Although this is only one study, it suggests that differing rates of bacterial vaginosis between racial groups may be due to cultural differences rather than genetic and socio-economic variations.

Contraceptive practice

Swedish and Belgium studies found significant associations between bacterial vaginosis and the use of intrauterine devices compared with oral contraceptive or barrier contraceptive users[37,38]. However, when comparing intrauterine device users to non-contraceptive users the same studies failed to find an association[14,37,38]. Two American studies recorded significantly increased risks of bacterial vaginosis in intrauterine devices than non-contraceptive users, but the results may not be relevant to the UK as contraceptive practices and guidelines for antibiotic use after intrauterine devices insertion differ between the two countries. Intrauterine device use has also changed considerably over time decreasing significantly in the 1980s in the United States[5,39,40]. Bacterial vaginosis is common among women over 30 years who are also the most likely to use an intrauterine device, meaning any association could be the result of the age structure of the study[29]. Since 6.6% of females of reproductive age in the UK use an intrauterine devices it is an important relationship to establish, especially as intrauterine devices use may become more widespread with the introduction of new hormone impregnated devices[29].

Sexual activity

Several risk factors studies for bacterial vaginosis have focused on whether it is a sexually transmitted infection. Although some studies have recorded associations between bacterial vaginosis and numbers of sexual partners and age at first intercourse, no consistent patterns have emerged (Table 2 and 3).

Risk factor studies of bacterial vaginosis in Sweden observed associations with higher numbers of sexual partners, lower age of first intercourse and previous history of a sexually transmitted infection characterising the epidemiological patterns of known sexually transmitted infections[7–9,39]. The number of partners in the last month was related to bacterial vaginosis, which was in turn linked to the frequency of partner change. Bacterial vaginosis often coincides with a new sexual partnership. Changes in the vaginal environment induced by sexual intercourse with a new partner may increase susceptibility to abnormal colonisation in certain women. The condition may simply follow disruption of the woman's established vaginal flora by intercourse with a new partner[9].

Bacterial vaginosis demonstrates a striking age profile opposing that seen for most sexually transmitted infections: there is a strong association of the presence of bacterial vaginosis with being of age over 25 that is unusual for most sexually transmitted infections in females where the highest rates are almost always in women younger than 25 years of age[14,25]. Women aged under 25 report higher numbers of sexual partners and higher rates of partner change, but report fewer cases of bacterial vaginosis opposing the proposed route of sexual transmission. However, this relationship may prove more complex as studies in women undergoing *in vitro* fertilisation treatment have found young women significantly more likely to have bacterial vaginosis [41,42].

Although bacterial vaginosis is more commonly found in sexually active women, it has been found in virgins[10,11].

A review of randomised controlled trials to assess the impact of treatment of partners of women diagnosed with bacterial vaginosis on cure rates found five of the six trials observed no benefit of partner treatment[43]. The

Table 2. Comparison of risk factors: associations of classical bacterial sexually transmitted infections (STI), such as with gonorrhoea and *chlamydia trachomatis*, and bacterial vaginosis (BV).

Associated risk factor	Classical STI	BV
Increasing no. of sexual partners	✓	✓
Lower age of first intercourse	✓	Inconsistent
Found in virgins	×	✓
Prevalence in lesbians	↓	↑
Appropriate partner treatment	Decreases prevalence	No relationship
Age	Highest prevalence in the under 25s	Highest prevalence in the over 25s
Smoking	✓	✓
Black ethnicity	✓	✓
IUCD use	✓	✓

Table 3. Risk factor studies of bacterial vaginosis. GUM = genitourinary medicine clinic; FPC = family planning clinic.

Country	Study population	Study design	Diagnostic method	Variables controlled for	Results	Author
Sweden	Pap smears	Retrospective cohort	Presence of clue cells	Age	BV associated with no. of lifetime sexual partners and a lower age of 1st intercourse	Larsson PG *et al.*, 1991[8]
	FPC outpatients	Prospective cohort	Clinical criteria	Multivariable	BV associated with higher no. of lifetime partners, higher no. partners in the last month and group sex	Nillson U *et al.*, 1997[9]
	FPC and youth clinics	Prospective cohort	Clinical criteria	Multivariable	BV associated with >1 partners in the last month and with casual sex	Shoubnikova *et al.*, 1997 [38]
	1ry health care clinic	Prospective cohort	Clinical criteria	Multivariable	No association of BV and age of 1st intercourse	Holst E *et al.*, 1987[4]
	GUM clinic	Prospective cohort	Clinical criteria	Multivariable	BV associated with age over 25; 5% increase in prevalence per 5yr age group	Moi H *et al.*, 1990[14]
UK	Antenatal	Prospective cohort	Gram stain	Multivariable	Sig more BV among smokers than non smokers	Hay PE *et al.*, 1994[15]
Sweden	FPC and youth clinics	Prospective cohort	Clinical criteria	Multivariable	Sig more BV in smokers than in non smokers	Shoubnikova *et al.*, 1997 [38]
	Health clinic	Prospective cohort	Clinical criteria	Multivariable	Sig more BV in smokers and former smokers than non smokers	Larsson PG *et al.*, 1991[8]
UK	Antenatal	Prospective cohort	Gram stain	Multivariable	Sig more BV among Afro-Caribbeans than Caucasians	Hay PE *et al.*, 1994[15]
USA	Medical centres	Prospective cohort	Gram stain, pH, culture	Multivariable	BV associated with black racial origin	Goldenberg *et al.*, 1996[32]
Sweden	GUM clinic	Prospective cohort	Clinical criteria	Multivariable	Sig more BV in IUD users than barrier contraceptive users. Sig less BV in barrier or OC users than in non users	Moi H *et al.*, 1990[14]
	FPC and youth clinics	Prospective cohort	Clinical criteria	Multivariable	Sig less BV in barrier or OC users than in non users. No association of BV with IUD use	Shoubnikova *et al.*, 1997[38]
	1ry health care clinic	Prospective cohort	Clinical criteria	Multivariable	BV associated with IUD only, no relation to other methods	Holst E *et al.*, 1987[4]
Belgium	GP	Prospective cohort	Discharge and clue cells	Multivariable	Sig more BV IUD use than OC use	Avonts D *et al.*, 1999[37]
USA	University students	Prospective, cohort	Clinical	?	BV associated with IUD use	Amsel R *et al.*, 1983[6]
	GUM	Prospective, cohort	Clinical	?	BV associated with IUD use	Lossick JG *et al.*, 1991[39]

exception observed that significantly more women were cured after two weeks if their partner had also received appropriate treatment. However, this result was only significant when diagnosing bacterial vaginosis by Gram stain; no such effect was found with diagnosis using the composite criteria[44].

Bacterial vaginosis is more prevalent among lesbians who usually report lower rates of sexually transmitted infection than the heterosexual population[45,46]. One American study found the likelihood of having bacterial vaginosis to be nearly 20 times greater in a lesbian relationship where the index partner had bacterial vaginosis, but a recent UK study failed to confirm the link between bacterial vaginosis and sexual activity among lesbians[47,48]. In a study of a self-selected group of lesbians in the United States 24.3% of the 115 women had flora consistent with bacterial vaginosis. Lactobacilli were only detected in 61% of all women and the overall prevalence of H_2O_2 producing lactobacilli was low at 40%[46]. It is possible that the low prevalence of H_2O_2 lactobacilli accounts for the high rates of bacterial vaginosis among this population. Further investigation of the sexual practices underlying that state is needed.

Avonts *et al.*[37] compared rates of bacterial vaginosis in women using intrauterine device and oral contraceptives attending a general practice consecutively over a two-year period. The risk of bacterial vaginosis increased with the number of sexual partners in the oral contraceptive users (OR 5.5, 95% CI 1.7-17.5 for two or more partners compared with one). No such relationship was found among the intrauterine device users (OR 0.8, 95% CI 0.2-7.8) suggesting that host factors are more important than sexual intercourse in the acquisition of bacterial vaginosis.

Conditions and complications associated with bacterial vaginosis

Bacterial vaginosis is responsible for considerable morbidity among reproductive age women. It has been consistently associated with preterm delivery, but its role in upper genital tract infection (pelvic inflammatory disease), tubal damage and infertility is less certain.

Preterm delivery

Forty percent of preterm births are associated with an infective aetiology, but it is unclear how much of this could be classified as bacterial vaginosis. Prospective studies have reported attributable risks of between two and ten for bacterial vaginosis in pregnancy leading to preterm delivery rising to over 30 in women with a history of a previous preterm birth[49,50]. It has been suggested that the production of endotoxins by the bacterial vaginosis microflora stimulate susceptibility, in certain women, to the cascade of cytokines and prostaglandins that initiate labour[51]. Many studies have only found a statistically significant association when restricting analyses to women considered as at a high risk of preterm delivery. This has been highlighted by several randomised controlled trials, investigating the potential health gains to be made from treating bacterial vaginosis during pregnancy. The picture may become clearer through the results of the multicentre ORACLE trial which aims to investigate the association of subclinical infection with preterm labour and the effect of broad spectrum antibiotic treatment on the rate of preterm birth[52].

Tubal infertility

Several UK studies have investigated the association between bacterial vaginosis and tubal infertility after noting that the prevalence of bacterial vaginosis tends to be higher in women attending infertility clinics than among the general population[42]. Two recent studies in women undergoing IVF in Glasgow and Bristol found women with tubal infertility to have significantly higher rates of bacterial vaginosis than those with non-tubal infertility[53,54]. In another observational study Wilson *et al.*[42] found that one-third of women with tubal factor infertility had bacterial vaginosis, compared with 16% where male factor infertility was diagnosed, and around 19%–21% with other causes of infertility. The excess of bacterial vaginosis with tubal infertility was significantly greater than for male factor infertility (OR 3.23 95% CI 1.99-5.25). If there is a causative relationship between bacterial vaginosis and tubal infertility or pelvic inflammatory disease there are issues of the direction of the cause and effect.

Miscarriage

Miscarriages are most likely to occur during the first trimester of pregnancy. Consequently, many remain unreported, as the pregnancy may not have been registered at an antenatal clinic, leaving any association with bacterial vaginosis unclear[55]. Significantly higher rates of miscarriage are also known to occur among black women[56–58]. This is only weak evidence of an association with the relationship potentially confounded by age, parity, education and socio-economic status.

A study of miscarriage in the first trimester of pregnancy in women undergoing IVF showed that of those conceiving, the women with bacterial vaginosis at conception had a significantly increased risk of miscarriage (crude OR 2.49, 95% CI 1.21 to 5.12). This association remained significant after the adjustment of other factors known to increase the risk of miscarriage including maternal age and smoking. However, it is hard to know how this increased risk translates to women in the population who are able to conceive naturally[41].

Miscarriage causes substantial psychological morbidity. The risk of an episode of a major depressive disorder

was 2.5 times greater in women in the 6 months following a miscarriage compared with community controls in a US study[59]. If a link between miscarriage and bacterial vaginosis is proven, treatment in pregnancy could prevent many cases of depression.

Pelvic inflammatory disease

The similarity in micro-organisms characteristic of both bacterial vaginosis and pelvic inflammatory disease makes an association between the two and progression from bacterial vaginosis to pelvic inflammatory disease in the absence of sexually transmitted infection biologically plausible. Studies have found bacterial vaginosis to be more common among women with pelvic inflammatory disease and have isolated organisms associated with bacterial vaginosis in the upper genital tract. However, this does not prove causality, nor does it indicate how much pelvic inflammatory disease is attributable to bacterial vaginosis[14,60–62]. A study by Eschenbach *et al.*[12] found a ninefold increased risk of pelvic inflammatory disease in women with bacterial vaginosis than controls among 640 randomly chosen women attending genitourinary medicine clinic, but this used an insensitive clinical diagnosis of adnexal tenderness to diagnose pelvic inflammatory disease. A threefold increase in risk for pelvic inflammatory disease was recorded by Peipert *et al.*[63] using what they regard as the gold standard of laparoscopy for the diagnosis of pelvic inflammatory disease. However, there were only 116 women enrolled in the study of whom just 25 were bacterial vaginosis positive.

Endometrial infection is thought to precede ascending infection of the fallopian tubes. Several studies have used endometrial biopsies to investigate the relationship between plasma cell endometritis and bacterial vaginosis. Korn *et al.*[64] found plasma cell endometritis to be more frequently present in women with bacterial vaginosis than without (OR 15, 95% CI 2-686), although only 22 women were diagnosed with bacterial vaginosis and without another cervical infection. Hillier *et al.*[65] observed the anaerobic gram rods associated with bacterial vaginosis to be independently associated with endometritis.

One causative pathway may be via a termination of pregnancy as this has been reported as a risk factor for pelvic inflammatory disease in women with bacterial vaginosis with the biological mechanism being the introduction of the organisms into the upper genital tract[66–68]. The diagnosis of pelvic inflammatory disease is difficult and, given the number of organisms with the potential for causing it, elucidating the role of bacterial vaginosis will be very difficult.

Cervical intraepithelial neoplasia

Cervical intraepithelial neoplasia (CIN) has a multifactorial aetiology, it is associated with sexual activity, and can lead to carcinoma of the cervix, the most powerful cause being oncogenic human papillomavirus infection. Any association between bacterial vaginosis and CIN is suggested to be caused by nitrosamines produced by the abnormal vaginal microflora[69,70]. A retrospective study[71] of 300 patients at a UK genitourinary medicine clinic found significantly more bacterial vaginosis in women with CIN, but other studies have failed to confirm these findings[72–75]. Only two studies diagnosed bacterial vaginosis using the composite criteria and Gram staining, but they took place in different clinical settings and reached opposite conclusions[71,73].

Bacterial vaginosis and HIV susceptibility/infectivity

The presence of bacterial vaginosis increases susceptibility to human papillomavirus (HIV) infection, as with bacterial sexually transmitted infections[76,77]. *Gardnerella vaginalis* lysates have been shown to stimulate HIV expression *in vitro* in monocytoid and certain T cell lines[78]. A recent study in Chicago collecting cervicovaginal lavage specimens found Gram stains indicative of bacterial vaginosis to be significantly associated with a newly identified HIV-inducing factor that induces HIV-1 gene expression[79].

Studies carried out in high HIV-1 prevalence populations in Africa have found bacterial vaginosis to be more prevalent among women who are HIV positive. A study in Uganda reported an odds ratio for HIV-1 of 2.08 (95% CI 1.48-2.94) in women with severe bacterial vaginosis (score of 9-10 on a Gram stain) compared with those with normal vaginal flora[24,25]. However, more recent analyses from that study have suggested that any effect of bacterial vaginosis is far less than the effect of viral load in determining the risk of heterosexual transmission between discordant couples (couples where initially only one is infected with HIV). A cohort study in HIV negative pregnant women in Malawi found that women with bacterial vaginosis were significantly more likely to seroconvert before giving birth (OR 3.7, $P = 0.03$), as well as after giving birth (OR 2.3, $P = 0.04$)[80]. A further prospective cohort study among sex workers in Kenya showed women with abnormal flora on Gram's stain to be at an increased risk of HIV-1 acquisition (HR = 1.9, 95% CI 1.1-3.1). During follow up the absence of lactobacilli, characteristic of bacterial vaginosis, was also associated with an increased risk of HIV-1 (HR = 2.0; 95% CI 1.2-3.5) suggesting a protective role of lactobacilli against vaginal infection[81].

There have been few studies in low HIV prevalence populations, but a cross sectional study of pregnant women in North Carolina found that those with abnormal vaginal flora were at an increased risk of HIV-1 seroconversion (RR 4.0, 95% CI 1.1-14.9)[82].

The Ugandan population-based study used mass antibiotic treatment with metronidazole but failed to reduce

both bacterial vaginosis and HIV-1 incidence[24,25]. The incidence of other STIs fell, but that of bacterial vaginosis only declined in the short term and then rapidly rose again. Failure to have an effect on HIV incidence may represent a failure to adequately treat bacterial vaginosis rather than a lack of a facilitory effect.

Potential for health gains

There are three areas of potential health gain from interventions for bacterial vaginosis: treating symptomatic cases, reducing sequelae such as infertility, pelvic inflammatory disease or HIV transmission and reducing infant mortality and morbidity associated with preterm birth.

The personal health burden felt by women with symptomatic bacterial vaginosis is considerable although unmeasured. The long term health burden in economic, social and psychological terms becomes even greater if the possible consequences of asymptomatic cases are included. Services for treatment need to be available. Currently the recommended treatment for bacterial vaginosis is 400mg of metronidazole taken twice daily for five to seven days, a 2g single dose of metronidazole, 5g of metronidazole 0.75% vaginal gel per night for five nights or 5g of 2% clindamycin cream intravaginally for seven days[83]. However, it is questionable whether these doses of antibiotic, duration of treatment and method of administration are optimal. Although short term cure rates are high, test-of-cure studies indicate that treatment with metronidazole or clindamycin is only effective in 66% of cases 4 weeks after treatment[84–86]. Treatment failure is probably not due to re-infection by a partner as no study has found this to occur[87]. Explanations for high treatment failure rates include that abnormal flora are just suppressed and not eradicated[85].

As bacterial vaginosis rarely interferes with work or domestic activity and the link to pelvic inflammatory disease and infertility remains unproven there is little public health support for mass or individual treatment. Intermittent mass therapy or regular individual treatment (of HIV negative women known to be at an increased risk of HIV-1 if bacterial vaginosis positive) might produce a benefit by reducing heterosexual HIV-1 transmission where this is intense. However, the Ugandan experiment had a negative result. Because of the apparent association between bacterial vaginosis and prematurity, screening and treating pregnant women for bacterial vaginosis or treating all women in pregnancy has been suggested to reduce the incidence of preterm births.

Cochrane review

The Cochrane collaboration carried out a systematic review to assess the effects of antibiotic treatment of bacterial vaginosis in pregnancy on the incidence of adverse neonatal outcomes[88]. The review considered randomised controlled trials comparing any antibiotic regimen for bacterial vaginosis with placebo or no treatment as well as studies comparing two antibiotic regimens among pregnant women of all ages at all stages of gestation. Five studies met the Cochrane criteria including three randomised controlled trials using oral metronidazole, one using oral amoxicillin and one using intravaginal clindamycin. The three RCTs comparing women treated with metronidazole or placebo observed a significant decrease in the risk of preterm birth amongst the treatment group[50,51,89]. No such decrease in risk was observed for the studies employing amoxicillin or clindamycin for treatment of bacterial vaginosis[90,91]. When the studies were analysed together in the systematic review it was found that of the 1050 women reviewed, antibiotic therapy given to the pregnant women with bacterial vaginosis was highly effective at eradicating the infection (0.22, 95% CI 0.17-0.27). There was, however, no reduction in the risk of preterm birth before 37 weeks of gestation with treatment for bacterial vaginosis (OR 0.78, 95% CI 0.60-1.02). The only significant decrease in risk of preterm birth came in the subset of women with a previous history of such an event (OR 0.37, 95% CI 0.23-0.60). This suggests that only screening and treating of those women with a history of a previous preterm birth might be of use.

Results from a large American trial of metronidazole to prevent preterm delivery among 1953 pregnant women with asymptomatic bacterial vaginosis were recently published. The women were randomised to receive treatment or placebo between 16-24 weeks of gestation and again at 24-30 weeks if infection persisted, but the study failed to show any treatment benefit[93].

The failure to prevent preterm birth in low risk women may be due to most women being treated after 20 weeks of gestation[50,51,89,92]. The relative risk of preterm birth associated with bacterial vaginosis decreases with gestational age. Treatment after the 20-week gestational stage may be inconsequential.

A recent UK randomised controlled trial among 400 women treated the majority before 16 weeks with intravaginal clindamycin and found a 5% reduction in preterm births in the treatment group[93]. This contrasts with the only other randomised controlled trial using intravaginal clindamycin in the US[91]. However, the latter treated women later in pregnancy once again suggesting the importance of early treatment.

Future research priorities

Epidemiological studies have been limited by inadequate methodology, although this reflects the difficult

and imprecise nature of bacterial vaginosis itself. A first step should be to increase our basic understanding of the vaginal flora and the factors that are associated with the changes and pathology of bacterial vaginosis. This would have implications for the optimal methods of diagnosis, treatment and prevention. Attempts are being made to supply a standardised case definition and recommend diagnostic criteria so that future case control studies will be more robust and comparable. The validation of clinical compared with microbiological diagnoses would help in assessing the robustness of studies. New methods of diagnosis should be investigated that could include the use of vulval swabs in association with new molecular techniques. The priority must be to establish diagnostic and management guidelines for use inpatient management systems.

The burden of morbidity resulting from bacterial vaginosis cannot be quantified until we have comprehensive UK prevalence estimates. Previous studies have concentrated on specific clinic populations. A multicentre general practitioner-based study (building on the first UK prevalence study of bacterial vaginosis in general practice[28]), covering the general population would provide more complete and representative prevalence data. This should be used to investigate differences related to race and whether these are genetically or socially determined.

Bacterial vaginosis has yet to be shown as an independent risk factor for pelvic inflammatory disease, infertility and miscarriage in the absence of sexually transmitted infections. If proven, a causal relationship between bacterial vaginosis and upper genital tract morbidity would increase the public health profile of bacterial vaginosis. Cohort studies are needed to understand the natural history of infection and to quantify the risk of complications associated with infection. A randomised controlled trial following women with bacterial vaginosis in treatment and placebo groups and the incidence of upper genital tract sequelae might help determine the relationship between bacterial vaginosis and pelvic inflammatory disease and/or infertility.

Randomised controlled trials have indicated the potential health gains to be made through the early treatment (i.e. before 20 weeks) of pregnant women who have previously experienced a preterm birth. However, comprehensive trials are needed to establish that the treatment of bacterial vaginosis does lead to a decrease in reproductive morbidity among all groups of women. The questions of the optimal antibiotic, dose and length of treatment remain unanswered. Large-scale trials within antenatal populations should be extended and start early in pregnancy (e.g. 12 weeks). Randomised controlled trials should also be used to elucidate the most effective treatment options. These trials must be followed by robust economic analyses to quantify the possible health gains.

Conclusions

Prevalence studies indicate that there is a potentially large reservoir of bacterial vaginosis infection in the population. Given the high proportion of asymptomatic cases, prevalences are likely to be under-estimated by most studies. Bacterial vaginosis is linked to sexual activity but is distinct from other sexually transmitted infections. As such, classical preventive methods for sexually transmitted infections may have little impact on the transmission of bacterial vaginosis.

At present bacterial vaginosis can be definitively linked to preterm birth and increased risk of HIV-1 acquisition. Future confirmation of a causative role in upper genital tract infection and infertility can only increase its public health profile.

Epidemiological studies have been limited by the use of variable case definitions and diagnostic methods among heterogeneous populations. Morbidity studies have been limited by their cross sectional nature preventing the establishment of a causative relationship. Robust epidemiological data are essential for effective disease control providing a basis for intervention design, resource allocation and targeting those at risk.

Effective treatment is available, although optimal doses and treatment lengths have yet to be confirmed. Once questions concerning the acquisition and aetiology of infection have been addressed, high risk groups could be targeted more efficiently. Such advances will finally allow the UK population prevalence and proportion of reproductive morbidity directly attributable to bacterial vaginosis to be uncovered so that an accurate assessment of the true public health significance of bacterial vaginosis can be made.

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