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Association between bacterial vaginosis or chlamydial infection and miscarriage before 16 weeks' gestation: prospective community based cohort study

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Abstract

Objectives To assess whether bacterial vaginosis or chlamydial infection before 10 weeks' gestation is associated with miscarriage before 16 weeks.

Design Prospective cohort study.

Setting 32 general practices and five family planning clinics in south London.

Participants 1216 pregnant women, mean age 31, presenting before 10 weeks' gestation.

Main outcome measure Prevalence of miscarriage before 16 weeks' gestation.

Results 121 of 1214 women (10.0%, 95% confidence interval 8.3% to 11.7%) miscarried before 16 weeks. 174 of 1201 women (14.5%, 12.5% to 16.5%) had bacterial vaginosis. Compared with women who were negative for bacterial vaginosis those who were positive had a relative risk of miscarriage before 16 weeks' gestation of 1.2 (0.7 to 1.9). Bacterial vaginosis was, however, associated with miscarriage in the second trimester at 13-15 weeks (3.5, 1.2 to 10.3). Only 29 women (2.4%, 1.5% to 3.3%) had chlamydial infection, of whom one miscarried (0.32, 0.04 to 2.30).

Conclusion Bacterial vaginosis is not strongly predictive of early miscarriage but may be a predictor after 13 weeks' gestation. The prevalence of *Chlamydia* was too low to assess the risk, but it is unlikely to be a major risk factor in pregnant women.

Introduction

Miscarriage is the most common adverse outcome of pregnancy. It causes psychological and physical morbidity and incurs considerable costs to the NHS. Bacterial vaginosis is associated with miscarriage after 16 weeks' gestation and with preterm birth but its role in early clinical pregnancy loss has never been properly investigated in healthy women in the community.^{1,2} The effect of chlamydial infection during pregnancy is also unclear.³ It is important to know whether these infections are associated with early miscarriage because treatment might be preventive. Equally, if there is no evidence of an association or possible treatment benefit, the risks related to screening and treatment may be avoided.

We aimed to test the hypothesis that the risk of clinically recognised miscarriage before 16 weeks' ges-

tation is increased in women with bacterial vaginosis or chlamydial infection detected before 10 weeks' gestation. We also aimed to determine if the risk of miscarriage related to infection depends on duration of gestation.

Methods

We invited 34 general practices and five family planning clinics in south London to take part in our study. We gave the practices and clinics posters, laminated protocols, patient information sheets, and specimen packs and asked them to recruit consecutive pregnant women presenting before 10 weeks' gestation. We excluded women intending to have a termination. Women who gave informed consent were asked to provide a self administered vaginal swab, vaginal smear, and first pass urine sample immediately and to complete a confidential postal questionnaire at 16 weeks' gestation. The questionnaire asked about personal characteristics, medical history, and pregnancy outcome.

Vaginal smears were stained by Gram's method and examined for bacterial vaginosis.¹ Flora were graded as normal (no *Gardnerella vaginalis* present), intermediate, or bacterial vaginosis. Swabs and urine samples were tested for *Chlamydia* by ligase chain reaction assay. Positive results were confirmed by direct immunofluorescence. Women were defined as *Chlamydia* positive if they had a confirmed positive result on either a swab or a urine specimen.

Gestation was calculated from the first day of the last menstrual period, if known, and modified when necessary after ultrasound examination. A miscarriage was defined as any report of clinically recognised miscarriage after a positive pregnancy test that occurred before 16 weeks' gestation. At 16 weeks' gestation we informed the women's general practitioners or doctors at the family planning clinics of the results of the infection screen.

We used Cox regression to calculate the relative risk of miscarriage in women with bacterial vaginosis compared with those who were negative or intermediate for bacterial vaginosis. This allowed for variable gestation at recruitment or miscarriage. We adjusted for recognised risk factors for miscarriage: increasing

Table 1 Characteristics of 1201 pregnant women according to bacterial vaginosis status at recruitment

Characteristic	No (%)	Prevalence (proportion) of bacterial vaginosis among women		Relative risk (95% CI)	Age adjusted relative risk (95% CI)¶
		Women with characteristic	Women without characteristic		
Age <25 (n=1201)	150 (12.5)	22.6 (34/150)	13.3 (140/1051)	1.7 (1.2 to 2.5)**	—
Afro-Caribbean or black African (n=1096)	116 (11.1)	33.6 (39/116)	11.1 (109/980)	3.0 (2.1 to 4.4)***	2.9 (2.0 to 4.2)***
Social class 3 to 5† (n=1036)	415 (40.0)	16.5 (68/415)	10.5 (65/621)	1.6 (1.1 to 2.2)**	1.5 (1.0 to 2.1)*
Single, widowed, or divorced (n=1095)	94 (8.58)	28.7 (27/94)	11.6 (116/1001)	2.5 (1.6 to 3.8)***	2.3 (1.5 to 3.7)***
Previous oral contraception or none (n=1085)	683 (62.9)	14.8 (101/683)	10.7 (43/402)	1.4 (1.0 to 2.0)	1.4 (1.0 to 2.0)
No previous pregnancies (n=1094)	388 (35.5)	11.1 (43/388)	15.2 (107/706)	0.7 (0.5 to 1.0)	0.7 (0.5 to 1.0)
Smoked during this pregnancy‡ (n=786)	117 (14.9)	17.1 (20/117)	10.8 (72/669)	1.6 (1.0 to 2.6)	1.4 (0.9 to 2.4)
Previous termination of pregnancy (n=1087)	270 (24.8)	21.9 (59/270)	10.7 (87/817)	2.1 (1.5 to 2.9)***	2.0 (1.5 to 2.8)***
Previous miscarriage§ (if ever been pregnant n=700)	225 (32.1)	16.0 (36/225)	14.9 (71/475)	1.1 (0.7 to 1.6)	1.1 (0.7 to 1.6)
Previous preterm birth at <37 weeks (if ever been pregnant n=700)	39 (5.6)	10.3 (4/39)	15.2 (101/661)	0.7 (0.3 to 1.8)	0.7 (0.3 to 1.8)
Concurrent chlamydial infection (n=1199)	29 (2.4)	44.8 (13/29)	13.8 (161/1170)	3.3 (1.9 to 5.7)***	2.8 (1.6 to 5.0)***

*P<0.05, **P<0.01, ***P<0.001.

†For women who were unemployed or students, partner's social class was used when available.

‡Questions on smoking were omitted from questionnaires at start of study.

§13 women had had ≥3 miscarriages.

¶Adjusted for age <25 or ≥25.

age, history of miscarriage, and smoking during pregnancy.

Results

Between June 1998 and July 2000, 1216 pregnant women, mean age 31 (range 16-48), were recruited. The median gestation at recruitment was 49 days (range 12-69). Ascertainment of pregnancy outcome at 16 weeks was 99.8% (1214 of 1216). Overall, 88% (1069) of women returned the questionnaire.

The prevalence of bacterial vaginosis was 14.5% (174 women, 95% confidence interval 12.5% to 16.5%). A further 4.5% (54) of women were intermediate for bacterial vaginosis. Bacterial vaginosis was more common in women under 25, those of Afro-Caribbean or black African ethnic group, those in social classes 3-5, single women, those who had previously used oral contraception or none, those who smoked during pregnancy, those with a history of termination, and those with concurrent chlamydial infection (table 1). The overall prevalence of chlamydial infection was 2.4% (29 of 1214, 1.5% to 3.3%), but 8.5% (13 of 152, 4.1% to 12.9%) in women under 25 and 14.3% (6 of 42, 3.7% to 24.9%) in teenagers.

Miscarriage related to bacterial vaginosis or chlamydial infection

Overall, 121 women (10.0%, 8.3% to 11.7%) miscarried before 16 weeks' gestation. The relative risk of miscarriage before 16 weeks in women who were positive for bacterial vaginosis compared with those who were

negative or intermediate was 1.15 (0.70 to 1.87) (table 2). This relative risk did not change substantially when adjusted for risk factors for miscarriage—age over 37 (1.11, 0.68 to 1.81), history of miscarriage (1.34, 0.76 to 2.35), and smoking during pregnancy (1.04, 0.54 to 2.03)—or when adjusted for concurrent chlamydial infection (1.20, 0.74 to 1.97). Bacterial vaginosis was, however, associated with miscarriage in the second trimester at 13-15 weeks (3.45, 1.16 to 10.29). The interaction between gestational age at miscarriage and bacterial vaginosis status on the Cox regression was significant ($\chi^2_{2df}=13.10$; $P<0.01$).

Only one of 28 women with chlamydial infection miscarried (0.32, 0.04 to 2.30; when adjusted for bacterial vaginosis this was 0.30 (0.04 to 2.14)). Miscarriages before 16 weeks' gestation were more common in women over 37 (3.14, 1.98 to 4.98) and in those with a history of miscarriage (1.76, 1.12 to 2.76).

Discussion

Bacterial vaginosis is not a strong predictor of miscarriage before 16 weeks' gestation. However, the risk of miscarriage related to bacterial vaginosis status depends on length of gestation.

Strengths and weaknesses of study

Our study is unique as it was prospective and designed specifically to look at the relation between genital infection and early miscarriage in a community based cohort of healthy women. The community setting enabled us to recruit and screen women much earlier

Table 2 Outcome of pregnancy at 16 weeks' gestation related to bacterial vaginosis status at recruitment in 1189 women. Values are numbers (percentages) unless stated otherwise

	Bacterial vaginosis status			Relative risk (95% CI) of miscarriage if positive†
	Positive (n=170)	Intermediate (n=54)	Negative (n=965)	
Any miscarriage	19 (11.2)	5 (9.3)	97 (10.1)	1.15 (0.70 to 1.87)
Gestation time of miscarriage:				
<10 weeks	4 (2.4)	2 (3.7)	45 (4.7)	0.53 (0.19 to 1.47)
10-12 weeks	10 (5.9)	1 (1.9)	45 (4.7)	1.32 (0.67 to 2.62)
13-15 weeks	5 (2.9)	2 (3.7)	7 (0.7)	3.45 (1.16 to 10.29)*
Still pregnant at 16 weeks	144 (84.7)	48 (88.9)	863 (89.4)	
Termination of pregnancy at known date‡	7 (4.1)	1 (1.9)	5 (0.5)	

*P<0.05.

†Calculated with Cox regression. Women positive for bacterial vaginosis compared with women negative or intermediate combined.

‡Date of termination unknown in further 9 women who decided to have termination after enrolment.

in pregnancy than studies based in hospitals. Our study is the largest of its kind to date, achieved despite difficulties of recruiting from inner city settings, and ascertainment at 16 weeks was over 99%. The women who completed questionnaires at 16 weeks' gestation were unaware of the results of their infection screen. In addition we showed that screening in primary care is feasible by self administered vaginal swabs even during pregnancy and by using only routine specimen storage and transport facilities. Finally, our finding that miscarriage was more common in women over 37 and in those with a history of miscarriage is similar to other studies.^{4 5}

The main limitation of our study was that the low overall prevalence of chlamydial infection meant that we could not adequately evaluate any relation between *Chlamydia* and miscarriage. Our study was powered primarily to look at the influence of bacterial vaginosis rather than chlamydial infection on miscarriage. However, the low prevalence of chlamydial infection showed that it is unlikely to be a major risk factor for miscarriage in this population. This may not apply to pregnant teenagers, in whom the prevalence of *Chlamydia* was 14%. Our study is also the first to show that chlamydial infection in early pregnancy is associated with an almost threefold increase in the risk of bacterial vaginosis, independent of age.

Implications

Because bacterial vaginosis is not a strong risk factor for miscarriage before 16 weeks' gestation, it seems unlikely that screening and treatment of asymptomatic bacterial vaginosis would improve miscarriage rates, particularly in the first trimester. One reason may be because around 65-90% of clinically recognised early miscarriages are due to chromosomal abnormalities, and the occurrence of such abnormalities correlates strongly with maternal age.⁶ However, our results suggest that bacterial vaginosis is associated with miscarriage in the second trimester. The mechanism may be ascending spread of infection followed by an inflammatory response.⁷ Although in our cohort these late miscarriages comprised only 12% (14 of 121) of the total, they may be particularly traumatic. In one study 12% of women who had a miscarriage in the second trimester had a major depressive disorder in the following six months.⁸

Our study also shows that non-invasive screening for bacterial vaginosis and chlamydial infection using self administered vaginal swabs is feasible in pregnant women in the community. This might be important for prevention of adverse outcomes related to infection later in pregnancy and could involve collaboration between primary care and secondary care.^{3 9}

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What is already known on this topic

Miscarriages are common and associated with considerable morbidity and costs

Bacterial vaginosis is associated with miscarriage after 16 weeks' gestation and preterm birth but the role of chlamydial infection is uncertain

What this study adds

Bacterial vaginosis is not a strong predictor of miscarriage before 16 weeks' gestation but may be associated with miscarriage at 13-15 weeks' gestation

The prevalence of chlamydial infection was too low for it to be a major risk factor for miscarriage in this population of healthy pregnant women

Non-invasive screening for bacterial vaginosis and chlamydial infection by using self administered vaginal swabs is feasible in pregnant women in the community

manufacture 2% clindamycin vaginal cream. He has conducted clinical trials for which his unit has received reimbursement from Osmetech, 3M, Pharmacia, and Upjohn, and he has received financial support to attend conferences for these companies.

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Endpiece

The noble profession

Medicine, the only profession that labours incessantly to destroy the reason for its existence.

James Bryce (1838-1922),
English diplomat and author;
ambassador to the United States, 1907-13

Submitted by Hannah Josty,
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