

Articles

Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomised controlled trial

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Summary

Background Abnormal vaginal flora and bacterial vaginosis are associated with amplified risks of late miscarriage and spontaneous preterm delivery. We aimed to establish whether antibiotic treatment early in the second trimester might reduce these risks in a general obstetric population.

Methods We screened 6120 pregnant women attending hospital for their first antenatal visit—who were at 12–22 weeks' gestation (mean 15.6 weeks)—for bacterial vaginosis or abnormal vaginal flora. We used gram-stained slides of vaginal smears to diagnose abnormal vaginal flora or bacterial vaginosis, in accordance with Nugent's criteria. We randomly allocated 494 women with one of these signs to receive either clindamycin 300 mg or placebo orally twice daily for 5 days. Primary endpoints were spontaneous preterm delivery (birth ≥ 24 but < 37 weeks) and late miscarriage (pregnancy loss ≥ 13 but < 24 weeks). Analysis was intention to treat.

Findings Nine women were lost to follow-up or had elective termination. Thus, we analysed 485 women with complete outcome data. Women receiving clindamycin had significantly fewer miscarriages or preterm deliveries (13/244) than did those in the placebo group (38/241; percentage difference 10.4%, 95% CI 5.0–15.8, $p=0.0003$). Clindamycin also reduced adverse outcomes across the range of abnormal Nugent scores, with maximum effect in women with the highest Nugent score of 10.

Interpretation Treatment of asymptomatic abnormal vaginal flora and bacterial vaginosis with oral clindamycin early in the second trimester significantly reduces the rate of late miscarriage and spontaneous preterm birth in a general obstetric population.

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Introduction

In the developed world, preterm delivery is the leading cause of perinatal morbidity and mortality and childhood neurodevelopmental delays and deficits.^{1–3} Data exist linking bacterial vaginosis with preterm delivery.⁴ Intermediate abnormality of the vaginal flora, regarded as a transitional stage between normal vaginal flora and bacterial vaginosis,⁵ is also associated with a 3–5-fold increase in risk of mid-trimester pregnancy loss.^{6–8} Results of studies of systemic antibiotic treatment of bacterial vaginosis in women at high risk of preterm delivery suggest treatment reduces risk of subsequent preterm birth.^{8–10} These studies, however, were either small,⁹ overly dependent on subgroup analysis,¹⁰ or were not randomised.⁸ In two randomised controlled trials, short courses of oral metronidazole administered late in the second trimester (23–24 weeks' gestation) did not reduce frequency of preterm delivery in women with bacterial vaginosis who were at low risk of this outcome.^{11,12} Intravaginal clindamycin treatment in pregnancy eradicated bacterial vaginosis but failed to reduce risk of preterm delivery,^{13–15} possibly because intravaginal drugs might not be effective against organisms in the endometrial cavity.¹⁶

Bacterial vaginosis is associated with subclinical endometritis,¹⁶ which may create an adverse endometrial milieu for the developing embryo or fetus. This link might partly account for the reported association between bacterial vaginosis or intermediate flora and first trimester miscarriage.¹⁷ Furthermore, women at greatest risk of preterm delivery are those in whom bacterial vaginosis is diagnosed in early rather than late pregnancy.¹⁸ Therefore, initiation of systemic antibiotic treatment early might offer the best chance of modifying the risks associated with abnormal vaginal flora and bacterial vaginosis.

We therefore did a randomised, placebo-controlled, double-blind trial with the aim to establish whether screening for and treating asymptomatic bacterial vaginosis and intermediate abnormal flora early in the second trimester reduces the risks of late miscarriage and preterm delivery in an unselected population of pregnant women.

Participants and methods

Participants

From Nov 1, 1996, to Feb 1, 1999, all pregnant women who booked for antenatal care at St George's Hospital, London, UK, and St Helier Hospital, Surrey, UK (from May 1, 1997), were sent an information leaflet describing abnormal vaginal flora and bacterial vaginosis and our trial, before their first attendance. Screening for abnormal vaginal flora and bacterial vaginosis was offered to all women at their first antenatal clinic visit if they were between 12 and 16 weeks pregnant, by their menstrual date or early ultrasound scan. Women who were screen-positive were invited to discuss the trial in greater detail within 10 days of screening, and those consenting and meeting the study's inclusion criteria were randomly allocated to a treatment group. By 20 months, because

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our recruitment rate was below target, we modified entry criteria to include women who were over 16 weeks, but less than 22 weeks, pregnant.

Women were excluded from the trial if they had any of the following: multiple pregnancy; needed or had cervical cerclage; history of cone biopsy; uterine, cervical, or fetal anomaly; disorders such as diabetes, renal disease, collagen disease, lupus, antiphospholipid syndrome, or essential hypertension; known allergy to clindamycin; or were younger than 16 years of age. Women who reported a fishy smelling vaginal discharge, either voluntarily or on direct questioning, received treatment and further genitourinary screening for sexually transmitted pathogens, but were excluded from randomisation.

Every participant discussed the trial with one of the investigators (AU) and provided written consent. The local research ethics committees at both centres approved the study.

Procedures

We did a routine ultrasound scan at 20–22 weeks' gestation to confirm gestational age and to screen for congenital and chromosomal anomalies. The gestational age was revised and the scan date used if there was a discrepancy of more than 7 days between the scan and menstrual dates.

Each woman herself did the screening test following instruction, by insertion of a swab (pure viscose tip; Technical Service, Heywood, UK) about 3–4 cm into the vagina.¹⁹ The swab was then withdrawn and smeared on a clean glass slide (SuperFrost; R A Lamb, Eastbourne, UK) identified by her name, hospital number, and date of birth. Slides were air-dried, gram-stained within 5 days, and two investigators (AU and PH) assessed the slides with the Nugent scoring system.²⁰ Nugent scores of 0–3 were graded as normal flora, 4–6 as intermediate abnormal flora, and scores of 7–10 as bacterial vaginosis.⁶ The two investigators read the first 700 slides together over a 6-month period until interobserver variation was negligible. Subsequently, PH reviewed all slides graded as abnormal by AU and 10% of those graded as normal.

We used a computer program to randomly assign the numbers 1–500 to clindamycin or placebo treatment. A trial pharmacist used this randomised list to package bottles of 5-day courses of either clindamycin (300 mg) or placebo, to be taken twice daily. The clindamycin capsules were identical to and indistinguishable from the placebo capsules. The investigators received these pre-packaged bottles identified only as numbers 001–500 and allocated the bottles consecutively to the study participants. Neither the participants nor the investigators knew the contents of any of the pre-packed bottles. The trial pharmacist retained the code for group allocation within a sealed envelope until all study data had been obtained and analysed.

We advised women to discontinue treatment if they developed abdominal cramps, vomiting, or diarrhoea, and to contact the investigators. All participants attended a follow-up clinic 2–4 weeks after treatment and were questioned about any side-effects, occurrence of thrush, and the status of their pregnancy. The rest of their care continued according to the local antenatal practice.

We extracted data on gestational age at delivery, birthweight, sex of the infant, admission to the neonatal intensive care unit, and antibiotic treatment from hospital records.

We defined miscarriage as spontaneous expulsion of the products of conception either before 13 completed weeks of gestation (early miscarriage) or between 13 or more and less than 24 weeks (late miscarriage) in a clinically recognised pregnancy. Miscarriage was confirmed either by amenorrhoea and positive pregnancy test, ultrasound scan of intrauterine pregnancy structures, histological demonstration of products of conception after evacuation, or a combination of these. We defined spontaneous preterm birth as delivery of the neonate at or beyond 24 weeks of gestation, but before 37 completed weeks, as a result of spontaneous onset of labour or rupture of membranes.

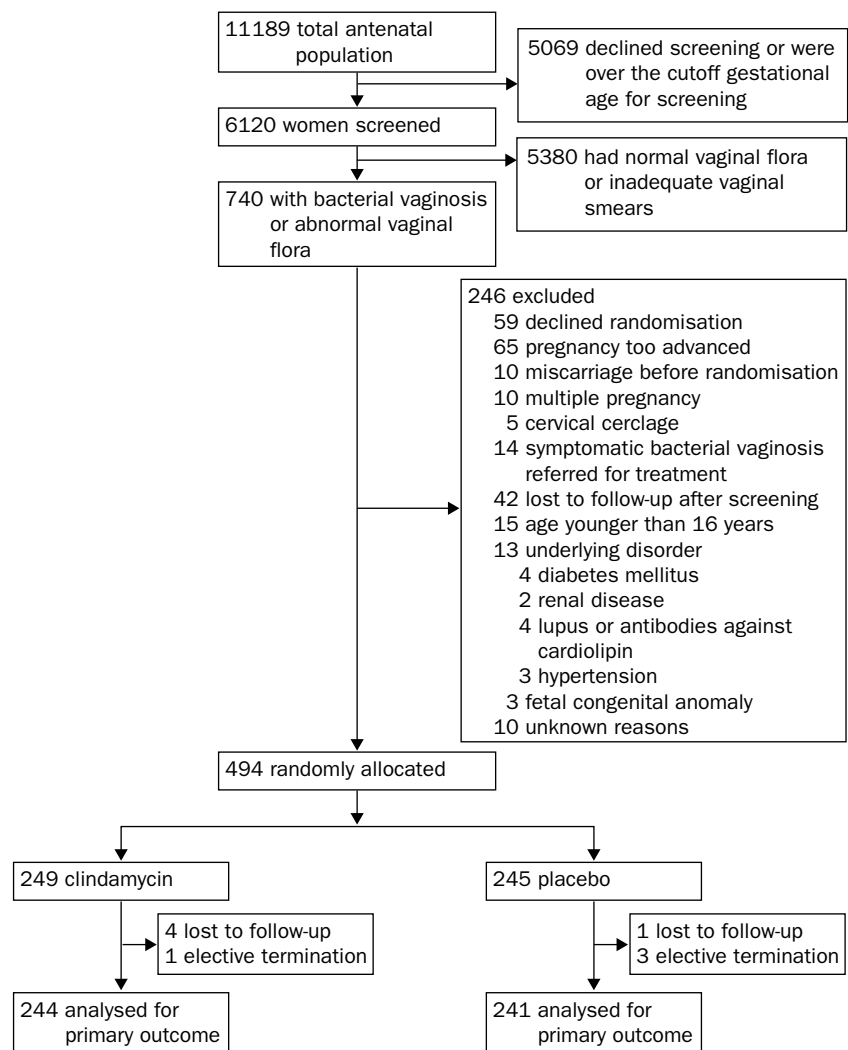


Figure 1: Trial profile

	Clindamycin group (n=244)	Placebo group (n=241)
Baseline characteristics		
Age (years, mean [SD])	28.8 (5.6)	28.5 (5.4)
Parity (mean [SD])	0.8 (1.1)	0.8 (1.0)
Gestation at randomisation (weeks, mean [SD])*	15.6 (2.6)	15.7 (2.6)
Ethnic origin		
White	155/241 (64%)	144/237 (61%)
Black African	25/241 (10%)	24/237 (10%)
Black Caribbean	36/241 (15%)	42/237 (18%)
Asian	16/241 (7%)	20/237 (8%)
Other	9/241 (4%)	7/237 (3%)
Nugent score		
Intermediate flora (4–6)	37 (15%)	38 (16%)
Bacterial vaginosis (7–10)	207 (85%)	203 (84%)
Previous miscarriage		
Any	63/240 (26%)	80/234 (34%)
2nd trimester, any	15/240 (6%)	20/234 (9%)
1st trimester, only	48/240 (20%)	60/234 (26%)
Previous spontaneous preterm delivery	24/235 (10%)	22/233 (9%)

Data are mean (SD) or number of participants (%). Data are missing for some patients' characteristics. *Three participants randomised below 12 weeks' gestation were instructed to commence treatment at 12 weeks.

Table 1: Participants' baseline characteristics

Statistical analysis

Our main a-priori hypothesis was that there would be a fall in the percentage of late miscarriages and spontaneous preterm deliveries in the treatment group. Sample-size calculations showed that 239 women in each of the treatment and placebo arms would detect a difference of 9% in the percentage of women having second-trimester miscarriage or spontaneous preterm delivery, decreasing from 15% in the placebo group⁶ to 6% in the treatment group, with 90% power and a 5% significance level. To allow for dropouts, we aimed to recruit 250 women in each group.

We compared categorical variables between treatment and placebo groups with Fisher's exact test, and continuous variables with the *t* test. Time to delivery, miscarriage, or last known follow-up is presented for each group by Kaplan-Meier survival curves. These curves include women lost to follow up, who were excluded from all other analyses (follow-up times: 16, 17, 28, and 34 weeks in the clindamycin group; 20 weeks in the placebo group).

Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit the report for publication.

Results

Of 11 189 pregnant women booked for antenatal care at the two centres over the trial period, 6120 (54.7%) were screened. Of these, 740 (12.1%) tested positive for abnormal intermediate vaginal flora or bacterial vaginosis, of whom 494 (78 abnormal intermediate flora, 416 bacterial vaginosis) were randomly allocated to receive either clindamycin (249) or placebo (245). 246 women were excluded for reasons shown in figure 1. Five women who were lost to follow-up after randomisation could not be traced despite searches through the records of their registered family doctor, health authorities' relocation and transfer records within and outside our own health region, and attempts to trace their next of kin, including telephone calls to overseas countries. Four women had elective terminations of pregnancy after randomisation. Results presented are for the remaining 485 women in the study. Baseline characteristics of these women are shown in table 1.

One woman ingested only the first 300 mg of clindamycin and miscarried on the same day but was included in the analysis. Another woman had an intrauterine death at 38 weeks' gestation, with *Clostridium difficile* isolated from the fetus. This woman received placebo. 25 women (5%) had side-effects and discontinued therapy; eight took placebo and 17 clindamycin. Side-effects included any gastrointestinal upset (n=15 [ten placebo, five clindamycin]; nausea, vomiting, diarrhoea, abdominal pains, or a combination of these), rashes (two [one placebo, one clindamycin]); vulvo-vaginal candidiasis (two [one placebo, one clindamycin]), throat irritation (one [placebo]), and headaches (five [one placebo, four clindamycin]). The clindamycin group had a slightly higher, but non-significant, rate of reported side-effects (table 2).

Four women (two clindamycin, two placebo) were treated with antibiotics for sexually transmitted infections (two chlamydia, two gonorrhoea). Of these, one had a spontaneous preterm delivery (placebo) and the others had term deliveries. 12 women (eight placebo, four clindamycin) received antibiotic treatment for other indications before onset of labour. All were included in the analysis.

Outcomes of pregnancy are shown in table 2. Women receiving clindamycin had significantly fewer miscarriages or spontaneous preterm deliveries than did women who received placebo (13/244 [5.3%] vs 38/241 [15.7%]; percentage difference 10.4% [95% CI 5.0–15.8], *p*=0.0003). Nine of the spontaneous preterm deliveries were between 24 and 32 weeks' gestation (three clindamycin, six placebo), and 30 were between 33 and 36 weeks (eight clindamycin, 22 placebo). Seven of 11 elective preterm deliveries were due to pre-eclampsia (five clindamycin, two placebo; table 3). Mean gestational age overall (including deliveries and miscarriages) did not differ significantly between groups (table 2; *p*=0.052). No significant difference between groups was seen in the proportions of babies admitted to the neonatal intensive care unit or in the mean birthweight for delivered babies. Figure 2 shows the cumulative proportion of women who miscarried, delivered, or were lost to follow-up at each week of gestation, for each group.

	Clindamycin group (n=244)	Placebo group (n=241)	<i>p</i>
Outcome of pregnancy			
Spontaneous preterm delivery	11 (5%)	28 (12%)	0.001*
Late miscarriage	2 (1%)	10 (4%)	
Elective preterm delivery	8 (3%)	3 (1%)	
Death in utero	1 (<1%)	1 (<1%)	
Term delivery	222 (91%)	199 (83%)	
Admission to neonatal intensive care unit	18/238 (8%)	23/228 (10%)	0.41
Side-effects reported	17/239 (7%)	8/239 (3%)	0.10
Birthweight†			
Low (<2500 g)	20/240 (8%)	23/227 (10%)	0.53
Very low (<1500 g)	10/240 (4%)	4/227 (2%)	0.18
Gestation at delivery (weeks, mean [SD])‡	38.8 (3.6)	38.0 (5.0)	0.052
Birthweight (g, mean [SD])‡	3227 (668)	3239 (637)	0.84

Data are number of participants (%) or mean (SD). **p* for all outcomes.

†Excludes 14 miscarriages and deaths in utero. ‡Includes 14 miscarriages and deaths in utero. Delivery includes miscarriages and deaths in utero.

Table 2: Pregnancy outcomes

Patient's number (treatment group)	Gestational age at delivery (weeks)	Birthweight (g)	Pre-eclampsia	HELLP	IUGR	Reduced amniotic fluid	Abnormal doppler ultrasound	Abnormal cardiotocography	Mode of delivery	Lupus/ cardiolipin antibodies	Cervical cerclage
1 (C)	30	1120	-	-	+	+	+	-	ECS	-	-
2 (C)	32	1361	+	-	-	-	-	-	ECS	-	-
3 (C)	29	820	+	-	+	+	+	+	ECS	-	-
4 (P)	36	1800	+	-	+	-	+	-	IOL, VD	-	-
5 (C)	31	1300	+	-	+	+	-	-	ECS	-	-
6 (C)	30	1230	+	-	-	-	-	-	ECS	-	-
7 (P)	33	2500	-	-	-	+	-	+	ECS	-	-
8 (C)	24	440	+	+	-	+	+	-	IOL, VD	-	-
9 (P)	34	1730	+	-	-	+	+	-	ECS	-	-
10 (C)	34	3280	-	-	LGA	-	-	-	ECS	-	-
11 (C)	26	930	-	-	-	-	-	-	VD	+	+

+=present; -=absent. C=clindamycin; P=placebo; ECS=emergency caesarean section; HELLP=haemolysis raised liver enzymes and low platelets; IUGR=intrauterine growth restriction; IOL=induction of labour; VD=vaginal delivery; LGA=large for gestational age. *Amniotic fluid increased. Participant 10 developed diabetes in pregnancy, fetal macrosomia or LGA, and polyhydramnios and was delivered prematurely for poor diabetic control. Participant 11 was diagnosed with antibodies against cardiolipin after randomisation and needed cervical cerclage on the basis of previous mid-trimester pregnancy loss. She ruptured her membranes at 25 weeks and the cervical stitch was removed. Spontaneous preterm delivery followed at 26 weeks.

Table 3: Clinical details and indications for delivery of 11 women with elective preterm delivery

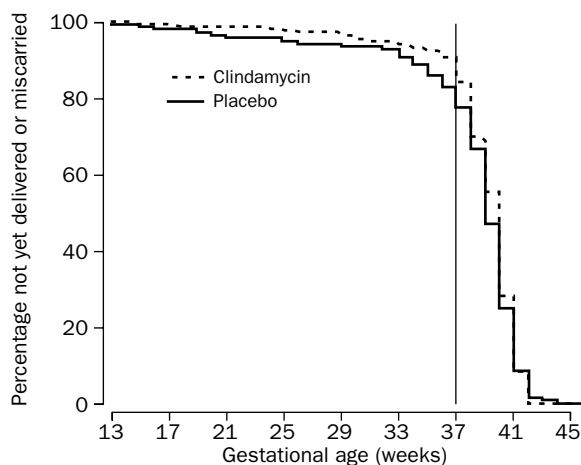
Table 4 shows the possible effect of other variables on the efficacy of clindamycin for women with bacterial vaginosis and abnormal intermediate flora. Our study was not designed to have sufficient power to do statistical analyses on subgroups or to test for interactions between variables, therefore these results are descriptive only. Women with a previous spontaneous preterm delivery or mid-trimester miscarriage had substantially worse outcomes overall. Clindamycin was associated with a reduction in the proportion of spontaneous preterm deliveries or late miscarriages both in women with and without previous history of spontaneous preterm birth and late pregnancy losses. It was also associated with a lower percentage of spontaneous preterm deliveries or late miscarriages across the range of Nugent scores for abnormal flora or bacterial vaginosis. However, the effect of treatment seems to be at a maximum in women with the most severe grade of bacterial vaginosis (Nugent score of 10): in this group, women who received clindamycin had a 5.4% rate of spontaneous preterm deliveries or late miscarriages compared with 35.7% in those who received placebo.

The proportion of spontaneous preterm deliveries or late miscarriages also fell substantially from a high baseline for women of Afro-Caribbean ethnic origin. However, ethnic

origin and Nugent score were not independent: 24% (19/78) of Afro-Caribbean women had a Nugent score of 10 compared with 14% (58/400) for all other ethnic origins combined. Results did not show a reduction in the rate of spontaneous delivery or late miscarriage in women of African origin, but numbers of women in this group were small.

Discussion

This study shows that treatment of asymptomatic intermediate abnormal vaginal flora and bacterial vaginosis in a general obstetric population reduces the occurrence of late miscarriage and spontaneous preterm delivery. To our knowledge, no previous studies have assessed the role of antibiotic treatment in reduction of risk of late miscarriage in pregnant women with abnormal vaginal flora. However, results of two randomised controlled trials of systemic metronidazole treatment in women at low risk of preterm delivery failed to show benefit from treatment.^{11,12} Our study differs from both trials in two respects. We initiated antibiotic treatment early in the second trimester and used a different regimen. We initiated treatment immediately at randomisation (mean gestation of 15.6 weeks), with 76% of the study population receiving antibiotic or placebo by 17 weeks. By contrast, McDonald and colleagues¹¹ administered antibiotics at 24 weeks, whereas Carey and co-workers¹² initiated antibiotic treatment at 23–24 weeks' gestation (average of 4 weeks after randomisation).



Number of women	Clindamycin	248	246	246	242	239	232	222	69	0
Placebo	242	239	233	231	228	225	200	61	1	

Figure 2: Percentage of women not yet delivered or miscarried, by gestational age (Kaplan-Meier curves)

Line at 37 weeks' gestation represents the cutoff for premature delivery.

	Clindamycin group (n=244)	Placebo group (n=241)
Nugent score		
4	0% (0/2)	-
5	9% (1/11)	33% (3/9)
6	4% (1/24)	14% (4/29)
7	3% (1/38)	14% (4/28)
8	6% (6/100)	7% (7/100)
9	6% (2/32)	15% (5/33)
10	5% (2/37)	36% (15/42)
Previous preterm delivery or late miscarriage		
Yes	19% (7/36)	42% (16/38)
No	3% (6/199)	11% (21/195)
Ethnic origin		
White	3% (5/155)	14% (20/144)
Black Caribbean	8% (3/36)	33% (14/42)
Black African	12% (3/25)	8% (2/24)
Asian	6% (1/16)	10% (2/20)

Table 4: Difference in percentage of spontaneous preterm deliveries and miscarriages between treatment groups by factors that might affect outcome

Early introduction of antibiotic treatment also allowed us to study the effect of treatment on the frequency of late pregnancy losses. Since bacterial vaginosis is associated with subclinical endometritis,¹⁶ we postulated that risk of adverse pregnancy outcome might be established in early pregnancy, possibly even before implantation, and that early antibiotic treatment offered the best opportunity to reduce or prevent adverse sequelae. Furthermore, results of longitudinal follow-up studies have shown that spontaneous resolution of bacterial vaginosis later in pregnancy is not associated with a reduction in risk of preterm birth,^{14,21} also suggesting that treatment at a late stage in pregnancy might not be beneficial.

The type, dose, and route of antibiotic used might be important with respect to outcome. We used oral clindamycin 300 mg twice daily for 5 days by contrast to the short courses of metronidazole used in other trials.^{11,12} The broader range of activity of clindamycin than metronidazole against bacterial vaginosis organisms, including the atypical mycoplasmas and *mobiluncus*,²²⁻²⁴ might make it more efficacious than metronidazole in treatment of endometritis. Clindamycin also has anti-inflammatory properties,^{25,26} which might be advantageous in limitation of the host inflammatory response. Its role in treatment of intermediate abnormal flora is less clear. Women with previous spontaneous preterm delivery or mid-trimester miscarriage had worse overall outcomes as we expected, but they also benefited from treatment in our study. This latter finding is lent support by results of some studies,^{10,11} but not by others.¹² The explanation for this discrepancy is not immediately apparent, but could be related to the type and dose of antibiotic.

Presence of *mobiluncus* confers the worst grade of abnormality of vaginal flora in the Nugent scoring system (ie, 9-10). The greatest absolute benefit of treatment was seen in women with the highest Nugent score of 10. In these women, rate of spontaneous preterm delivery and late miscarriage was reduced from 35.7% in the placebo group to 5.4% with treatment. This finding could suggest that the superior activity of clindamycin against *mobiluncus* compared with metronidazole is important.

In black women of Caribbean origin, the proportion of preterm deliveries and late miscarriages was substantially lower in the treated group than in the placebo group (8.3% vs 33.3%). Black women of African origin, on the other hand, were the only subgroup for whom a reduction in proportion of preterm deliveries and late miscarriages with clindamycin was not shown. These findings suggest that the black ethnic population might not be homogeneous, but our study is not sufficiently powered to draw firm conclusions.

The excess incidence of pre-eclampsia resulting in elective preterm delivery in women treated with clindamycin was unexpected, but numbers are very small (five clindamycin, two placebo). We are unable to explain this excess and can only attribute it to chance, since we have no evidence that bacterial vaginosis or its treatment with clindamycin would result in pre-eclampsia.

Our study has several potential limitations. First, data on the occurrence of preterm prelabour rupture of membrane was not systematically gathered, since this outcome was not defined at the design stage of the study. Nevertheless, retrospective review of the obstetric records of participants showed that all women who had this rupture delivered spontaneously before 37 completed weeks of gestation. At both trial centres, prelabour rupture of membrane was managed expectantly, with induction of labour at 37 weeks, or earlier if clinical chorioamnionitis supervened.

Second, randomisation did not perfectly balance the baseline history of previous early miscarriage between the treatment groups. 12 (5.6%) more women had early miscarriage in the placebo group than in the clindamycin group. However, this difference is unlikely to have accounted for our results, since previous history of first trimester miscarriage (unlike late miscarriage or preterm birth) is not associated with an amplified risk of subsequent late miscarriage or preterm delivery.^{27,28}

Finally, outcome data were not available for nine women who were lost after randomisation. Sensitivity analyses were done to assess the effect on our results if all five women in the clindamycin group had proceeded to either miscarriages or spontaneous preterm deliveries, and all four in the placebo group had proceeded to term deliveries; the main study comparison remained significant for all such scenarios (data available from authors).

In our study, the number of women with abnormal intermediate flora or bacterial vaginosis needed to treat to prevent one late miscarriage or spontaneous preterm delivery was ten. The optimum time to screen and treat is as yet unknown, and in view of our present knowledge, could well be pre-pregnancy. The characteristics of the women in our population might differ from those in other parts of the world, and thus our study needs replication in other settings.

Contributors

A Ugwumadu, I Manyonda, and P Hay contributed to design, collection of data, interpretation of results, and writing of the report. F Reid did the statistical analysis, and contributed to interpretation of results and writing of the report.

Conflict of interest statement

PH has received payment for lectures and consultancy from Osmetech, 3M, and Pharmacia and Upjohn, and has received funding for trials and to attend conferences from these companies.

Acknowledgments

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