

# Natural History of Bacterial Vaginosis and Intermediate Flora in Pregnancy and Effect of Oral Clindamycin

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**OBJECTIVE:** We sought to describe the natural history of abnormal vaginal flora in pregnancy and estimate the efficacy of oral clindamycin in eradicating it and preventing relapse.

**METHODS:** This was a subanalysis of a randomized trial of oral clindamycin for abnormal vaginal flora in pregnancy. All 494 enrolled women were asked to provide a vaginal smear 2 weeks after treatment and every second participant to provide further smears at 20, 24, 28, 32, and 36 weeks of gestation. We used Nugent score of Gram-stained smears to assess the cure rate among the clindamycin group and the rate of spontaneous resolution among the placebo group.

**RESULTS:** Posttreatment smears were available for 462 women (231 in each of the clindamycin and placebo arms). The prevalence of abnormal flora posttreatment was 10% (22 of 231) in the clindamycin group compared with 93% (214 of 231) in the placebo group ( $P < .001$ ). Two hundred nineteen women obtained 4 weekly smears; slides for 84 women were lost, and results were available for 135 women (69 clindamycin, 66 placebo). In the clindamycin group, the prevalence of abnormal flora was 15% at 20 weeks of gestation and 17% at 36 weeks of gestation compared with 69% at 20 weeks of gestation and 43% at 36 weeks of gestation in the placebo group.

**CONCLUSION:** Oral clindamycin eradicated abnormal flora in 90% of treated pregnant women and maintained a normal flora in two thirds of women throughout pregnancy. Almost one third of untreated women in our study had spontaneous resolution of abnormal flora by 20 weeks of gestation. Because previous research has shown that spontaneous resolution does not modify the risk of preterm birth, early screening is essential. (Obstet Gynecol 2004;

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**LEVEL OF EVIDENCE: I**

Bacterial vaginosis and intermediate flora (abnormal vaginal flora) increase the risks of chorioamnionitis,<sup>1</sup> midtrimester miscarriage, and preterm birth.<sup>2-4</sup> Although the natural history of abnormal vaginal flora in pregnancy is poorly understood, there are reports of spontaneous resolution in late pregnancy,<sup>5,6</sup> which may be explained in part by an increase in the concentration of protective *Lactobacillus* species in the vagina and a decrease in the populations of potentially pathogenic anaerobic bacteria that is known to occur in normal pregnancy.<sup>7</sup> This resolution, however, does not appear to alter the risk of preterm delivery,<sup>6,8</sup> suggesting that the risk of adverse outcome may be established early and therefore may not be reversible by subsequent spontaneous resolution or by late antibiotic treatment. This hypothesis might explain the failure of late oral metronidazole to reduce preterm delivery,<sup>9,10</sup> whereas oral and topical clindamycin therapy initiated early in the second trimester significantly reduced second-trimester miscarriage and preterm birth.<sup>11,12</sup> Knowledge of the natural history of abnormal vaginal flora in pregnancy is therefore important to further refine the optimal time to screen and treat women.

At present, there is no consensus on the antibiotic of choice for the treatment of abnormal vaginal flora in pregnancy, the optimal route and timing of therapy, and whether to treat persistent and recurrent cases. The aim of this study was to trace the natural history of abnormal vaginal flora in pregnancy in a group of placebo-treated

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pregnant women and estimate the cure rate of abnormal flora after oral clindamycin therapy and the risk of recurrence throughout pregnancy.

## MATERIALS AND METHODS

This study was a subanalysis of a larger randomized trial of oral clindamycin versus placebo initiated at a mean gestational age of 15.6 weeks for the treatment of abnormal vaginal flora in pregnancy.<sup>11</sup> In summary, pregnant women attending their first antenatal visit at St. George's Hospital, London, and St. Helier Hospital, Surrey, from November 1, 1996, through February 1, 1999, were offered screening for abnormal vaginal flora if they were between 12 and 22 weeks pregnant according to their menstrual date or early ultrasound scan. Women who had positive test results were invited to participate, and those consenting and meeting the study's inclusion criteria were randomly assigned to a treatment group. Women were excluded from randomization if they had multiple pregnancy; needed or had cervical cerclage; had a history of cone biopsy; had a uterine, cervical, or fetal anomaly; had diabetes, renal disease, lupus, antiphospholipid syndrome, or hypertension; had an allergy to clindamycin; were aged less than 16 years; or reported a fishy-smelling vaginal discharge, in which case they received treatment and further genitourinary screening for sexually transmitted pathogens.

We used a computer program to randomly assign the numbers 1 to 500 to clindamycin or placebo treatment. A trial pharmacist used this randomized 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 and masked to the participants and investigators. The investigators allocated the bottles consecutively to the participants. The trial pharmacist retained the code for group allocation within a sealed envelope until all of the study data had been collected and analyzed. A total of 494 women was randomly assigned. The Local Research Ethics Committees at both centers approved the study.

Each participant received instruction on the technique of obtaining a self-administered vaginal smear. This was performed by inserting a Dacron swab approximately 4–5 cm into the vagina. The swab was left in the vagina for 10–15 seconds, rolled round through 360 degrees before withdrawal, and then smeared on a plain glass slide and air-dried. The slides were Gram stained and examined at the end of the study by 2 of the investigators (A.U. and P.H.) using the Nugent scoring system.<sup>13</sup> Nugent scores of 0–3 were graded as normal flora, 4–6 as intermediate flora, and scores of 7–10 were classified

as bacterial vaginosis.<sup>5</sup> The 2 observers had previously examined 700 Gram-stained slides of vaginal smears together until the interobserver variation between them was negligible.

All participants were given a swab and a slide and asked to obtain a vaginal smear for Gram stain assessment of the efficacy of treatment at 14 days after a 5-day course of oral clindamycin 300 mg or placebo twice daily. Each slide was labeled with the subject's trial number for identification and marked as "post treatment smear."

Because of resource constraints, every second participant enrolled in the randomized trial was invited to take part in a separate longitudinal follow-up study and instructed to obtain further vaginal smears at 5 time points (20, 24, 28, 32, and 36 weeks of gestation). Each slide was pre-labeled with the participant's trial number and the gestational age at sampling. If a participant declined, the invitation was extended to the next one. The slides were stored in a plastic slide carrier case by the participant until 36 weeks of gestation or earlier if preterm delivery occurred.

Abnormal vaginal flora is defined as persistent if the Nugent score of Gram-stained vaginal smear is 4 or greater at posttreatment assessment and at all time points of the longitudinal study. If normal flora was documented posttreatment, the subsequent detection of a Nugent score of 4 or greater by 36 weeks of pregnancy was counted as a relapse or recurrence.

Sample sizes originally were calculated to give sufficient power for the comparison of pregnancy outcomes between clindamycin and placebo groups within the randomized clinical trial.<sup>11</sup> A post hoc power calculation for this study indicates that the number of women who provided posttreatment vaginal smears (231 in each group) was sufficient to detect a difference of 10% in posttreatment cure rates between placebo-treated women (7%, observed) and clindamycin-treated women (17%), with 90% power at a 5% significance level. The Fisher exact test was used to compare categorical variables, and the *t* test used to compare continuous variables between the clindamycin and placebo groups.

## RESULTS

Of the 494 randomly assigned women, posttreatment vaginal smears and Nugent scores were available from 462, of whom 231 were in the clindamycin group and 231 in the placebo group. Table 1 shows the baseline characteristics of these women, who were well matched between the treatment and placebo groups for age, parity, ethnic origin, gestation at randomization, and pretreatment Nugent scores. Of the 32 women without



**Table 1.** Baseline Characteristics of the Treatment and Placebo Groups for All Women Providing Posttreatment Vaginal Smears

	Clindamycin group (n = 231)	Placebo group (n = 231)	P
Age (y)	28.8 (5.5)	28.5 (5.5)	.59
Parity	0.9 (1.1)	0.8 (1.0)	.44
Gestational age at randomization (wk)	15.4 (2.4)	15.6 (2.5)	.31
Ethnicity			
Caucasian	145 (64.4)	136 (60.4)	.72
Black African	24 (10.7)	21 (9.3)	
Black Caribbean	32 (14.2)	41 (18.2)	
Asian	16 (7.1)	20 (8.9)	
Other	8 (3.6)	7 (3.1)	
Pretreatment Nugent score			
Intermediate flora (4–6)	35 (15.2)	37 (16.0)	.90
Bacterial vaginosis (7–10)	196 (84.8)	194 (84.0)	

Age, parity, and gestational age are presented as mean (standard deviation); ethnicity and pretreatment Nugent scores are presented as n (%).

Nugent scores, 15 failed to return their slides, 9 slides could not be evaluated because of poor quality, 2 women miscarried before the time for posttreatment smear, 1 woman had elective termination of pregnancy, and no reason was documented for the remaining 5 women. At the posttreatment assessment (Table 2), only 10% (n = 22) in the clindamycin group compared with 93% (n = 214) in the placebo group had abnormal vaginal flora (difference = 83%, 95% confidence interval 78–88%,  $P < .001$ ).

Two hundred nineteen women (105 clindamycin, 114 placebo) participated in the longitudinal study, providing up to 5 slides at 20, 24, 28, 32, and 36 weeks of gestation. The slides for 84 women (36 clindamycin, 48 placebo) stored together were lost during the process of office relocation. The baseline characteristics of the remaining 135 women (69 clindamycin, 66 placebo), who provided one or more follow-up Nugent scores, were well balanced between the clindamycin group and the placebo group (Table 3). The results of the follow-up study of these women are presented in Table 4 and Figure 1. Not all women provided a full set of follow-up slides, and posttreatment scores were unavailable for 3 of these women (clindamycin group). Three women (1 clindamycin, 2 placebo) received antibiotic therapy for other indications but were included in the analysis.

In the clindamycin group, the low prevalence of abnormal vaginal flora achieved at 20 weeks of gestation (15%) was maintained throughout pregnancy (17% at 36

weeks of gestation). The prevalence of abnormal vaginal flora in the placebo group was 69% at 20 weeks of gestation (indicating spontaneous resolution in 31% of women by this time), steadily reducing to 43% at 36 weeks of gestation.

Of the 55 women in the clindamycin group who were cured posttreatment and also provided 1 or more follow-up slides, 12 (22%) showed evidence of recurrence at some point throughout the pregnancy, of whom 4 had intermediate flora, and 2 relapsed in gestational week 36 only. Forty-one women in the clindamycin group provided a posttreatment slide and a complete set of 5 follow-up slides: 4 (10%) had persistent abnormal vaginal flora (all of whom had term deliveries) and 27 (66%) had normal flora at all time points. Four women in this group showed improvement to normal flora, 3 deteriorated, and the remaining 3 subjects had fluctuating results over the course of time. In the placebo group, 49 women provided complete data, of whom 15 (31%) had persistent abnormal vaginal flora and 8 (16%) had normal flora at all time points. Seventeen women in this group improved over time without relapse, whereas the remaining 9 had fluctuating results.

## DISCUSSION

Fourteen days after treatment with a 5-day course of oral clindamycin, 90% of pregnant women with bacterial

**Table 2.** Posttreatment Nugent Scores

Status of vaginal flora (Nugent score)	Clindamycin group (n = 231)	Placebo group (n = 231)	P
Normal flora (0–3)	209 (90.5)	17 (7.4)	< .001
Intermediate flora (4–6)	8 (3.5)	34 (14.7)	
Bacterial vaginosis (7–10)	14 (6.1)	180 (77.9)	

Data are presented as n (%).



**Table 3.** Follow-Up Nugent Scores for the Clindamycin and Placebo Groups

Status of vaginal flora (Nugent score)	20 weeks of gestation (n = 54, 59)*	24 weeks of gestation (n = 64, 65)	28 weeks of gestation (n = 65, 65)	32 weeks of gestation (n = 65, 60)†	36 weeks of gestation (n = 65, 58)†
Normal flora (0–3)					
Clindamycin	46 (85.2)	53 (82.8)	53 (81.5)	53 (81.5)	54 (83.1)
Placebo	18 (30.5)	24 (36.9)	29 (44.6)	31 (51.7)	33 (56.9)
Intermediate abnormal flora (4–6)					
Clindamycin	4 (7.4)	5 (7.8)	6 (9.2)	5 (7.7)	2 (3.1)
Placebo	4 (6.8)	3 (4.6)	5 (7.7)	6 (10.0)	3 (5.2)
Bacterial vaginosis (7–10)					
Clindamycin	4 (7.4)	6 (9.4)	6 (9.2)	7 (10.8)	9 (13.8)
Placebo	37 (62.7)	38 (58.5)	31 (47.7)	23 (38.3)	22 (37.9)

Data are presented as n (%). The number of women in first the clindamycin group, then the placebo group, at each time point are given in the first row of the table.

\* Fewer follow-up slides were available at 20 weeks of gestation partly because a small number of women were not randomly assigned until 20–22 weeks of gestation.

† The lower number of women providing slides at 32 and 36 weeks of gestation in the placebo group is not due to higher levels of preterm delivery or miscarriage in this group; there were 3 deliveries prior to 36 weeks of gestation in the placebo group compared with 2 in the clindamycin group, and no miscarriages in either group.

vaginosis or intermediate vaginal flora reverted to normal flora compared with 7% of women who were treated with placebo. This cure rate is substantially higher than the 40–77% cure rates achieved with a 2-day course of oral metronidazole 400 mg taken twice a day and 2-g stat doses taken 48 hours apart.<sup>10,14</sup> It is also higher than the 60–80% elimination rates reported in studies that used topical clindamycin.<sup>15–17</sup> Furthermore, the prevalence of bacterial vaginosis throughout pregnancy is lower for oral clindamycin (7–14%) than the 38–58% reported in a comparable study that used oral metronidazole.<sup>14</sup> Available data suggest that women with persistent or recurrent bacterial vaginosis after topical treatment in pregnancy have a higher risk of preterm delivery than women treated with placebo.<sup>8</sup> Two controlled trials of oral metronidazole<sup>9,10</sup> and 4 of 5 such trials using intravaginal clindamycin therapy in pregnancy did not show a reduction in the risk of preterm delivery.<sup>8,12,15,17,18</sup>

Thus, we would suggest that oral clindamycin be considered the drug of choice for women with abnormal vaginal flora in pregnancy. It reduces the risk of late miscarriage and spontaneous preterm birth,<sup>11</sup> maintains normal vaginal flora in two thirds of treated women throughout pregnancy, and is well tolerated.

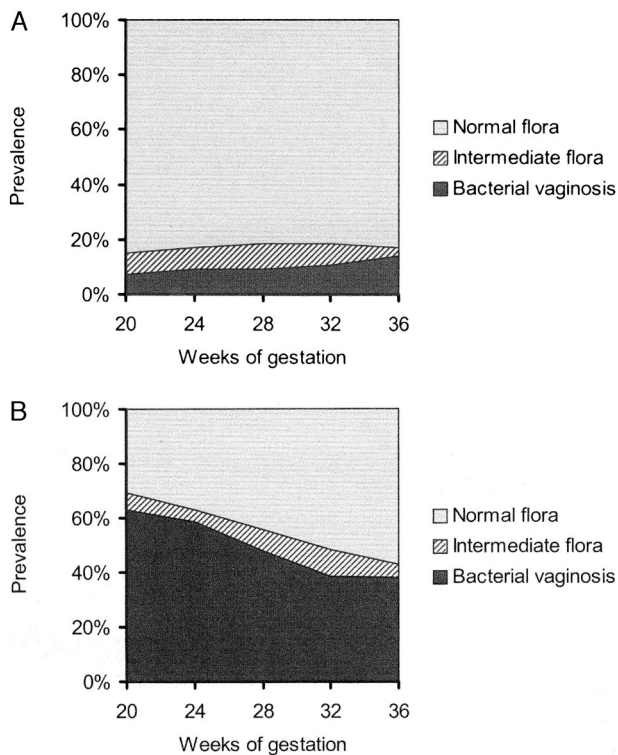
This study confirms the progressive decline in the prevalence of bacterial vaginosis in untreated pregnant women reported by previous studies<sup>5,6,14</sup> and extends this observation by documenting the earlier onset of spontaneous resolution in pregnancy. The 31% reduction in the prevalence of abnormal vaginal flora observed between recruitment (mean, 15.6 weeks) and 20 weeks of gestation suggests that approximately one third of women with abnormal vaginal flora would have a false-negative result if screening was initiated at 20 weeks of gestation or later, emphasizing the importance of early screening. This is further underpinned by the finding

**Table 4.** Baseline Characteristics of the Women Providing Follow-Up Smears Every 4 Weeks

	Clindamycin group (n = 69)	Placebo group (n = 66)	P
Age (y)	29.6 (4.8)	29.2 (5.2)	.66
Parity	0.7 (0.8)	0.6 (0.8)	.54
Gestational age at randomization (wk)	15.6 (2.7)	15.4 (2.4)	.72
Ethnicity			
Caucasian	47 (68.1)	43 (66.2)	1.00
Black African	6 (8.7)	7 (10.8)	
Black Caribbean	9 (13.0)	8 (12.3)	
Asian	4 (5.8)	4 (6.2)	
Other	3 (4.3)	3 (4.6)	
Pretreatment Nugent score			
Intermediate flora (4–6)	13 (18.8)	11 (16.7)	.80
Bacterial vaginosis (7–10)	56 (81.2)	55 (83.3)	

Age, parity, and gestational age are presented as mean (standard deviation); ethnicity and pretreatment Nugent scores are presented as n (%).





**Fig. 1.** Prevalence of bacterial vaginosis, intermediate flora, and normal flora in the (A) clindamycin and (B) placebo groups.

Ugumadu. *Bacterial Vaginosis in Pregnancy*. *Obstet Gynecol* 2004.

that the risk of preterm delivery associated with bacterial vaginosis is 2- to 6.9-fold higher in studies where bacterial vaginosis was detected before 20 weeks of gestation<sup>2,4,19</sup> compared with 1.4- to 1.9-fold increase reported in studies where it was diagnosed after 26 weeks of pregnancy.<sup>6,20,21</sup> It is probable that some abnormal flora might already have undergone spontaneous resolution even before the mean 15.6 weeks of gestation of randomization in this trial, raising the question of the optimal time to screen for and treat women for abnormal flora during pregnancy. A recent community-based study in south London screened women for bacterial vaginosis at less than 10 weeks of gestation. There was a significant association between bacterial vaginosis and miscarriage between 13 and 16 weeks of gestation but a nonsignificant trend for miscarriage between 10 and 13 weeks of gestation.<sup>22</sup>

We followed up women with vaginal smears 2 weeks after treatment and then every 4 weeks from 20 weeks of gestation. Changes other than those detected at the times of sampling could have occurred in the vaginal flora between the sampling times. Furthermore, we do not know for certain that women treated with oral clindamycin

were subsequently recolonized by the protective H<sub>2</sub>O<sub>2</sub>-producing strains of lactobacilli or that organisms within the endometrial cavity were definitely eradicated. We lost 84 sets of slides in an unfortunate office accident and were unable to compare the baseline characteristics of these women, thus raising the possibility of bias. The baseline characteristics of the remaining 66 women in the placebo group were, however, almost identical to those of the 69 women in the clindamycin group.

Our results suggest that screening for abnormal vaginal flora, if indicated, should be undertaken very early in pregnancy, perhaps at the beginning of the second trimester at the latest. Further studies are required to characterize the pregnancy specific stimuli that elicit the spontaneous resolution of abnormal vaginal flora in pregnancy, and the time of onset of their effect. Such data might hold the key for the development of effective interventions in future.

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