

## Bacterial Vaginosis

### **Importance**

Bacterial vaginosis is consistently linked to adverse pregnancy outcomes in well controlled research studies. Adverse outcomes include: spontaneous late or second trimester miscarriage, preterm birth, preterm rupture of membranes, low birthweight, chorioamnionitis, post partum endometritis, cesarean section wound infection, stillbirth, cerebral palsy and post abortion endometritis.<sup>1-6</sup>

### **Prevalence:**

Bacterial vaginosis is a common vaginal condition occurring in 12-40% of pregnant women.<sup>6</sup> Up to 80% of these women may be unaware of the presence of bacterial vaginosis.<sup>2</sup>

### **Characteristics:**

Bacterial vaginosis is characterized by high ( $10^8$  or greater) concentrations of potentially pathogenic bacteria, most notably *Prevotella* spp. (formerly *Bacteroides* spp.), *Peptococcus*, and *Mobiluncus* species, along with *Gardnerella vaginalis*, *Mycoplasma hominis*, and *Ureaplasma urealyticum*.<sup>1</sup> *Lactobacillus* spp. (especially hydrogen peroxide producing *L. jensenini*), which are normally present in high numbers in the vagina, are decreased in number or absent with the condition of bacterial vaginosis.<sup>1</sup> In addition, there are important alterations in the biochemical properties of bacterial vaginosis-associated vaginal fluid.<sup>2,3</sup> Biochemical changes include elevated pH, increased vaginal fluid concentrations of enzymes and organic compounds that may serve to overcome host defense mechanisms, as well as directly act on the cervical mucus, amniochorion and decidua to facilitate entrance of microorganisms into the upper reproductive tract and contribute to the initiation of preterm labor.<sup>2,3</sup> The pathophysiology of BV is shown in Figure 1.

### **Diagnosis:**

Currently, the recognized clinical gold standard is based on the presence of 3 of 4 clinical criteria (homogeneous, adherent, thin vaginal discharge;

vaginal fluid pH >4.5; release of amine odor with alkalinization of vaginal fluid; and presence of bacterial coated vaginal epithelial "clue" cells). A variety of other techniques have been developed for the diagnosis of bacterial vaginosis in order to decrease the subjectivity of the diagnosis. These include: combination of presence of clue cells on Papanicolaou smears with or without elevated vaginal fluid pH, gram stains of vaginal fluid interpreted using one of several systems, and biochemical analysis for sialidase levels.

### **Evidence**

#### **Bacterial vaginosis as a risk factor for preterm birth**

The influence of bacterial vaginosis on pregnancy outcome has been investigated through case-control, cross-sectional, prospective cohort studies, and randomized controlled treatment trials. Evidence from controlled clinical trials and meta-analyses are difficult to compare since studies often have the following differences:

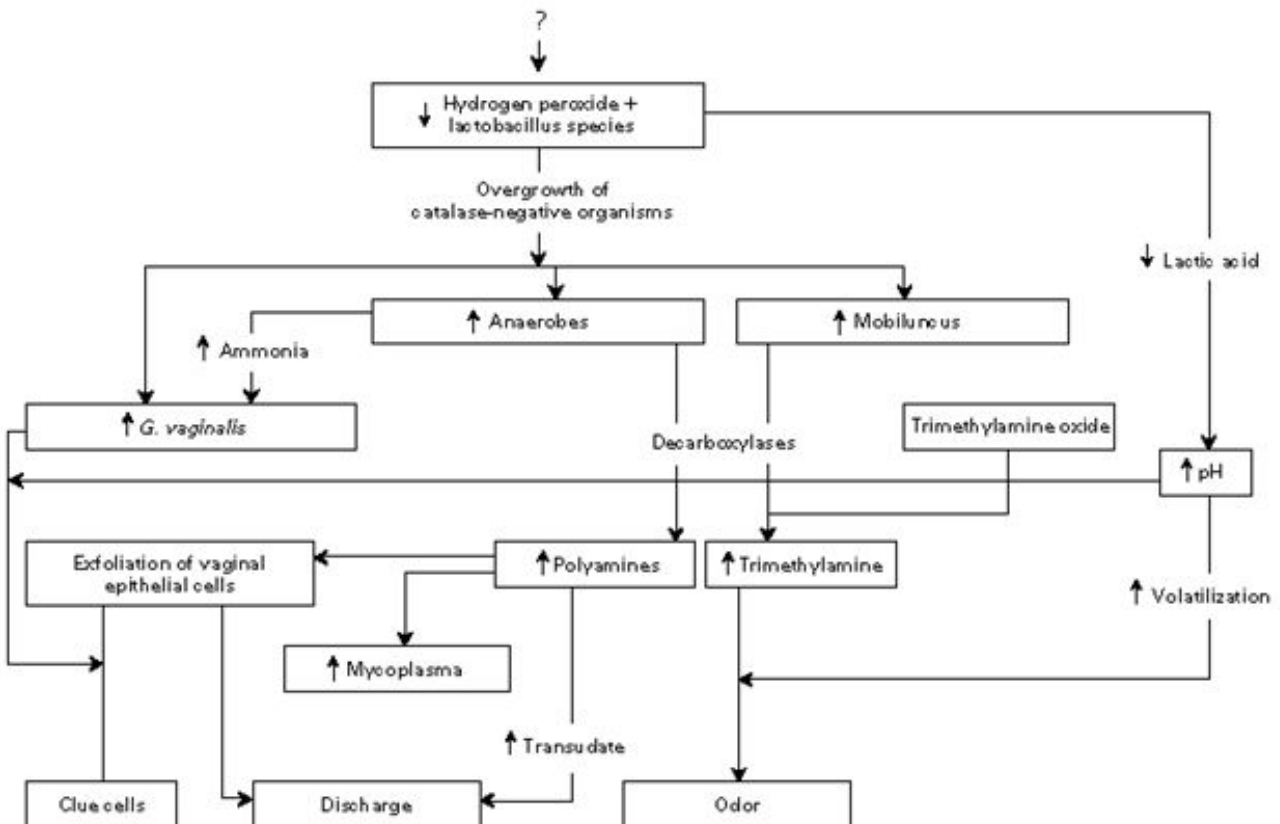
- Populations studied (i.e., geographic, and demographic characteristics)
- Risk status of enrolled clients (i.e., high risk due to prior PTB, social risk factors, low maternal weight, and positive fetal fibronectin, low risk women and women with and without BV)
- Gestational age at screening (i.e., ranges from 10 weeks to 32 weeks depending on the study)
- Tests used for diagnosis of BV (i.e., different sensitivity and specificity for detecting BV can bias study results towards showing no difference)
- Gestational age at treatment (i.e., trials using placebo "run-in" have one-month delay from screening to treatment)
- Treatment regimen (i.e., different drugs, different doses, different routes)
- Control for other infections or risk factors.

All but one meta-analysis demonstrate significant heterogeneity as studies are combined without consideration for these differences.

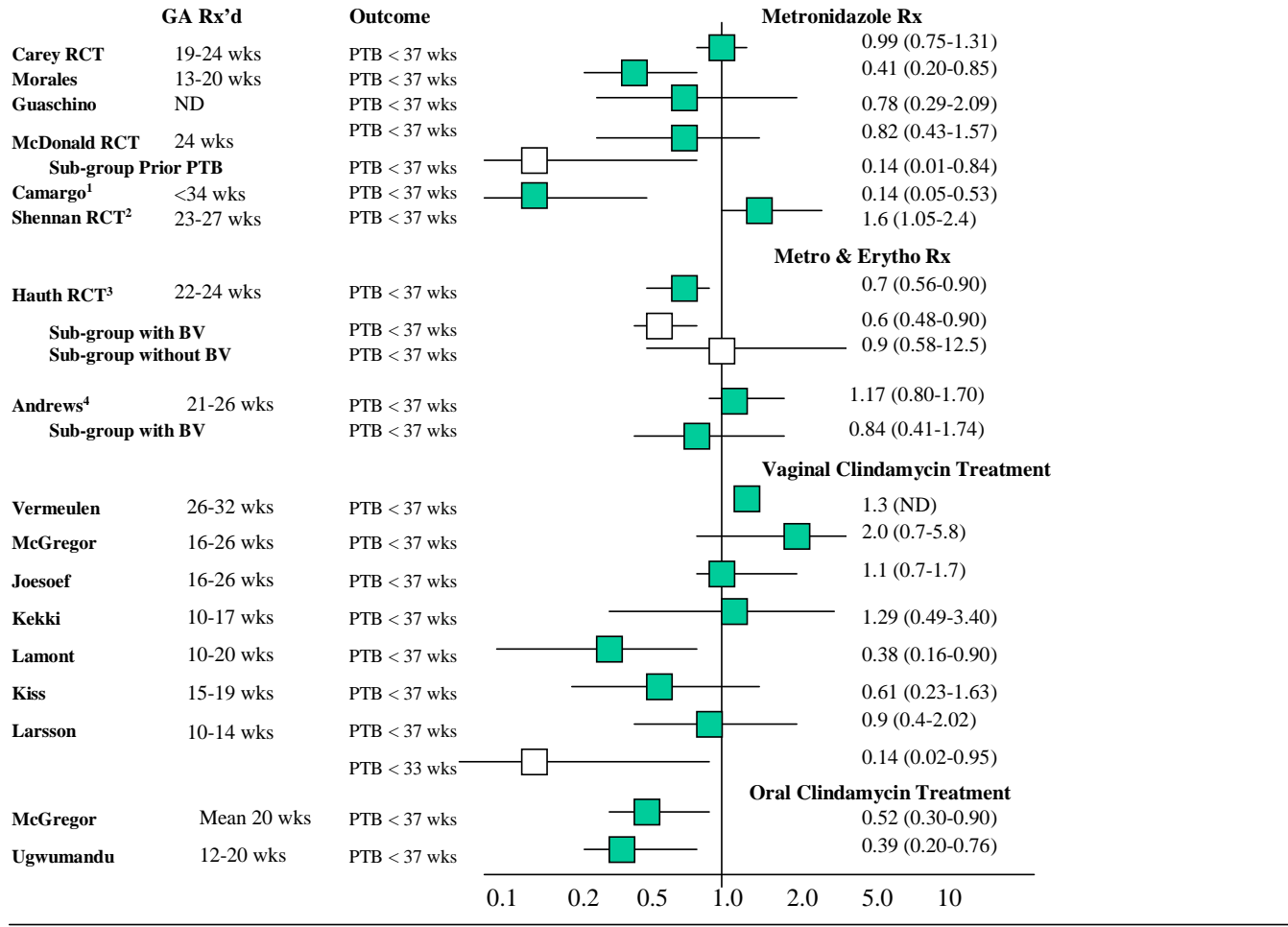
Studies that evaluated screening and treatment for BV to reduce PTB are listed in Figure 2 and summarized in Appendix 1.<sup>2-4,6-19</sup>

Taken together, two U.S. studies that used CDC-P recommended dosing regimens of oral metronidazole and one study from Australia using low dose metronidazole demonstrate reduced preterm birth among women at risk for preterm birth due to prior preterm birth or low maternal weight.<sup>4,6,7</sup>

A single large U.S. study did not show reduced preterm birth among unselected women receiving high doses of metronidazole in late second trimester.<sup>8</sup> Two studies which examined oral clindamycin show reduced preterm birth and/or late miscarriage among treated women.<sup>2,14</sup> Further these studies suggest that among women at increased risk for preterm birth, one preterm birth could be prevented for every three to six women treated at least prior to 24 weeks gestation, and among unselected women one preterm birth could be prevented for every ten to eleven women treated at 20 weeks gestation or less with oral clindamycin.<sup>2,14</sup>



## Antenatal Treatment Trials to Reduce Preterm Birth



1- Rx with Tinidazole and secnidazole

2- Pts enrolled for +fFN; Of 100 women randomized for + fFN-only 5 placebo and 8 treatment had BV

3- Pts enrolled for high risk due to prior PTB or Mat. Wt < 100 lbs

4- Pts enrolled for +fFN

Main Study Outcome Relative Risk  
 Subgroup Outcome Relative Risk

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- Trials enrolling women from the general population who are at average risk for preterm birth generally do not demonstrate any benefit to screening for and treating bacterial vaginosis.<sup>7</sup> The exception is a recent meta-analysis by Varma and Gupta<sup>20</sup> showing that screening and treatment of BV in women from low-risk population groups had a statistically significant reduction in spontaneous preterm delivery (nine trials, RR 0.73; 95% CI 0.55-0.98)
- Trials of women with a history of preterm delivery, on the other hand, show more promising results. For example, McDonald et al<sup>6</sup> had a 50% reduction in premature births in a subgroup of women who had a history of preterm delivery that was randomized to oral metronidazole.
- In general vaginal treatment regimens are less effective than oral treatment trials in preventing preterm birth, even though they are as efficacious in eradicating bacterial vaginosis.<sup>3,9-11</sup> The trial by Lamont et al<sup>12</sup> is an exception; they showed a statistically significant reduction in preterm birth (4% vs 10%) in women randomized to clindamycin vaginal cream at 13-20 weeks' gestation compared to placebo. Most recently, Larsson et al demonstrated a significant increase in gestational length among Swedish women treated with 2% clindamycin cream between 10 and 14 weeks gestation.<sup>18</sup> While Preterm birth before 37 weeks gestation was not significantly reduced, preterm birth at the earliest gestational ages (under 33 weeks) was reduced by over 85%.<sup>18</sup>

#### **Optimal Time for Screening:**

- Two studies suggest that early screening in the first trimester may be more useful in preventing preterm delivery than later screening. Hay et al<sup>5</sup> concluded that it is unusual for bacterial vaginosis to develop in pregnant women after 16 weeks of gestation. Moreover, early screening and treatment of bacterial vaginosis has been shown to be more effective at preventing preterm delivery than late screening and treatment. While there is debate about whether to screen and

treat asymptomatic women versus only symptomatic women, since the vast majority of women with bacterial vaginosis are asymptomatic, it seems reasonable to screen all women with an elevated vaginal pH (>4.5).

- The earlier BV is detected, the greater the risk of an adverse outcome. For example, BV at 26-32 weeks is associated with PTD odds ratio of 1.4-2 whereas BV at 7-16 weeks carries an OR of 5-7.5.<sup>21</sup>

It is widely held that organisms from the vagina ascend into the uterus during pregnancy, traversing the space between the membranes and the deciduas. The bacteria then take up residence in the membranes, and in about 50% of the cases enter the amniotic fluid. In a much smaller percentage of these cases, the fetus is infected as well. An alternate hypothesis is that the organisms that ultimately cause histologic chorioamnionitis actually reside in the uterus before pregnancy. Korn et al<sup>22</sup> observed that non-pregnant women who had bacterial vaginosis were nearly ten times more likely to have bacterial vaginosis-associated organisms residing in the uterus than were women who did not have bacterial vaginosis. These women were far more likely to have an associated chronic plasma cell endometritis. Andrews and coworkers<sup>23</sup> also observed a large number of bacterial vaginosis related organisms in the uterus in healthy non-pregnant women. These data suggest that there are women with bacterial vaginosis who have their endometrium colonized with bacteria before pregnancy. Most of these women are asymptomatic and would probably remain so until pregnant, because these colonizations do not seem to hinder conception and have little impact on pregnancy until the second trimester. Goldenberg et al<sup>24,25</sup> hypothesize that once the membranes become tightly applied to the deciduas, essentially forming an abscess, only then do these colonizations become symptomatic. With the adherence of the membranes to the deciduas at about 20 weeks gestation, the inflammatory

process accelerates, ultimately leading to late miscarriage or early preterm birth (usually before 28-30 weeks gestational age).

There is ample evidence suggesting that intrauterine infections are often chronic. Intrauterine infections have been documented weeks or even months before a preterm birth.<sup>26,27</sup> At the time of routine genetic amniocentesis at 16-18 weeks, cloudy amniotic fluid was occasionally noted and sent for culture. In nearly all cases in which the amniotic fluid was found to be infected with *Ureaplasma*, the women were initially asymptomatic; however, many of these women subsequently went on to spontaneously deliver at 24-28 week without clinical chorioamnionitis. The placentas, however, were nearly always positive for histologic chorioamnionitis. Similarly, using PCR-techniques for the diagnosis of *Ureaplasma* infection in the amniotic fluid, it has been demonstrated that women who are PCR-positive are substantially more likely to experience spontaneous preterm labor later in the second trimester.<sup>28</sup> More recently, using IL-6 as a marker of infection, it has been observed in several series that women undergoing routine genetic amniocentesis at 16-18 weeks and who are found to have high amniotic fluid IL-6 levels frequently deliver at less than 32 weeks.<sup>29-31</sup>

Between 50 and 100 different organisms have been associated with intra-uterine infections before the rupture of membranes. Some of the most commonly found organisms are *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Gardnerella vaginalis*, *Mobiluncus spp.*, *Peptostreptococcus spp.*, and *Prevotella spp.*, the same organisms involved in bacterial vaginosis. The organisms generally found in the uterus before delivery are of relatively low virulence. It may be that this low virulence accounts for both the chronicity described above and the fact that most of the intrauterine infections do not cause clinical chorioamnionitis.

#### Treatment of Bacterial Vaginosis:

The current CDC treatment recommendations are summarized below.<sup>32</sup>

- All pregnant women who have symptomatic disease require treatment.
- Some specialists prefer using systemic therapy to treat possible subclinical upper genital tract infections.
- Some specialists recommend the screening and treatment of asymptomatic pregnant women at high risk for preterm delivery. Such screening and treatment should be performed during the first prenatal visit.
- There is no evidence that metronidazole is teratogenic or mutagenic, and it is considered safe for use in pregnancy.
- Topical agents for the treatment of bacterial vaginosis in pregnancy are not recommended.

#### Recommended Regimens for Pregnant Women

Metronidazole 500 mg orally twice a day for 7 days

OR

Metronidazole 250 mg orally three times a day for 7 days

OR

Clindamycin 300 mg orally twice a day for 7 days.

#### Follow-Up of Pregnant Women:

Cure rates following oral therapy of bacterial vaginosis vary from 70-92%, whereas cure rates following vaginal therapy range from 33-86%. McGregor and coworkers clearly showed that cure depends on the timing of follow-up, with rates of 90% at 1 week and 60-70% at 4 weeks post-treatment.<sup>3</sup>

The CDC recommends that pregnant women treated for BV have a follow-up evaluation one month after completion of treatment to evaluate whether therapy was effective.

Sobel<sup>33</sup> notes that approximately 30% of patients with initial responses have a recurrence of symptoms within three months. The reasons are unclear; they include re-infection, but recurrence more

likely reflects vaginal relapse caused by failure to eradicate the offending organisms or to reestablish the normal protective vaginal flora dominated by lactobacillus. Management of symptomatic relapse includes prolonged therapy for 10-14 days.

Estimated impact of various infections on adverse pregnancy outcomes<sup>a</sup> through their effect on preterm birth<sup>34</sup>

Maternal infection/organism	Approx. maternal prevalence	Mothers infected (no.)	Estimated increase in PTB <sup>b</sup>	Estimated excess PTB <sup>c</sup> (no.)	Adverse outcomes linked to PTB <sup>d</sup>	
					Perinatal death (no.)	Neurologic sequelae (no.)
Bacterial vaginosis	20.0%	800,000	2X	80,000	4000	4000
Chlamydia	5.0%	200,000	2X	20,000	1000	1000
Gonorrhea	1.0%	40,000	3X	8,000	400	400
Syphilis	0.12%	4,800	2X	480	24	24
Trichomonas	2.0%	80,000	1.3X	2,400	120	120

<sup>a</sup> Assuming 4,000,000 births/year

<sup>b</sup> Based on best available data in untreated women

<sup>c</sup> Assuming a baseline preterm rate of 10%

<sup>d</sup> Assuming 5% deaths and 5% neurologic sequelae

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Treatment	Reference	Gestational age at treatment	Outcome	Group Analyzed	Number with Outcome/ Number Treated (%)	Number with Outcome/ Number of Controls (%)	Relative risk (95% CI)	Attributable Fraction (95% CI)	Number Needed to Treat
<b>Oral Medications</b>									
<b>High Risk Women</b>									
Metronidazole 500 mg twice daily for 7 days	Morales, 1994	13 to 20 weeks	Preterm birth	Intent to treat	8/44 (18%)	16/36 (39%)	0.4 (0.2-0.85)	ND	5
			Preterm PROM	Intent to treat	2/44 (5%)	12/36 (33%)	0.14 (0.03-0.57)	ND	4
			LBW	Intent to treat	6/44 (14%)	12/36 (33%)	0.42 (ND)	ND	ND
Metronidazole 250 mg three times daily for 7 days, Plus	Hauth, 1995	22 to 24 weeks	Preterm birth	Intent to treat	110/426 (31%)	68/190 (49%)	0.7 (0.56-0.90)	ND	6
Erythromycin 333 mg three times daily for 14 days;			Preterm birth	Subgroups: Without BV	56/254 (22%)	26/104 (25%)	0.9 (0.58-12.5)	NA	NA
			Preterm birth	With BV	54/172 (31%)	42/86 (49%)	0.6 (0.48-0.9)	ND	ND
Regimen repeated 2-4 weeks later for continued positive.			Preterm birth	Prior PTB	47/121 (39%)	32/56 (57%)	0.67 (0.5-0.9)	ND	ND
			Preterm birth	Weight < 50 kg	7/51 (14%)	10/30 (33%)	0.41 (0.18-1.0)	ND	ND
Metronidazole 400 mg twice daily for 7 days	Shennan, 2006	24 to 27 weeks	Preterm birth	Positive fFN	33/53 (62%)	18/46 (39%)	1.6 (1.05-2.4)	NA	NA
				Intent to treat				NA	NA
				Subgroup: With BV	ND/8	ND/5	ND		
<b>Mixed Risk Women</b>									
Metronidazole 400 mg twice daily at enrollment and repeated in 48 hours. Repeated at 4 wk follow-up if still positive.	McDonald, 1997	24 weeks and 28 weeks	Preterm birth	Intent to treat	20/429 (4.7%)	24/428 (5.6%)	0.82 (0.43-1.57)	NA	NA
			Preterm birth	Subgroup: Prior PTB	2/22 (9.1%)	10/24 (41.7%)	0.14 (0.01-0.84)	ND	ND



Treatment	Reference	Gestational age at treatment	Outcome	Group Analyzed	Number with Outcome/ Number Treated (%)	Number with Outcome/ Number of Controls (%)	Relative risk (95% CI)	Attributable Fraction (95% CI)	Number Needed to Treat
Metronidazole 2 gm once, and repeated in 48 hours; Repeated regimen between 24 and 29 wks.	Carey, 2001	At mean 19 weeks And 24 to 29 weeks	Preterm birth	Intent to treat	116/953 (12.2%)	121/966 (12.5%)	1.0 (0.7-1.5)	NA	NA
Clindamycin 300 mg three times daily for 7 days	McGregor, 1995	Mean 20 weeks	Preterm birth Preterm birth	Intent to treat BV	53/579 (9.5%) 9.8%	69/559 (12.6%) 18.8%*	0.75 (0.54-1.05) 0.52 (0.3-0.9)	ND ND	ND 11
Clindamycin 300 mg twice daily for 5 days	Ugwumadu, 2003	12 to 22 weeks	Preterm birth  Late SAB	Intent to treat  Intent to treat	11/244 (4.5%)  2/244 (0.8%)	28/241 (11.6%)  10/241 (4.1%)	0.39 (0.2-0.76)  0.2 (0.04-0.89)	43.9% (8.2%, 65.7%)  66.9% (-17%, 90%)	10  30

\* Observational control, not randomized; BV diagnosis by clinical criteria.



Treatment	Reference	Gestational age at treatment	Outcome	Group Analyzed	Number with Outcome/ Number Treated (%)	Number with Outcome/ Number of Controls (%)	Relative risk (95% CI)	Attributable Fraction (95% CI)	Number needed to treat
<b>Intravaginal Medications</b>									
<b>Women with BV</b>									
2% Clindamycin vaginal cream once daily for seven days	McGregor, 1994	16 to 26 weeks	Preterm birth		9/60 (15.0%)	5/69 (7.2%)	2.0 (0.7-5.8)	NA	NA
			PPROM		3/60 (5.0%)	3/68 (4.4%)	1.1 (0.2-5.4)	NA	NA
	Joesoef, 1995	16 to 26 weeks	Preterm birth < 37 weeks		51/340 (15.0%)	46/341 (13.5%)	1.1 (0.7-1.7)	NA	NA
			Preterm birth < 32 weeks		16/340 (4.7%)	9/341 (2.6%)	1.7 (0.7-3.9)	NA	NA
			LBW		30/334 (9.0%)	23/338 (6.8%)	1.2 (0.7-2.1)	NA	NA
	Kekki, 2001	10 to 17 weeks	Preterm birth		9/187 (5.0%)	7/188 (4.0%)	1.3 (0.49-3.4)	NA	NA
2% Clindamycin cream once daily for 7 days	Larsson, 2006	10 to 14 weeks	Preterm birth	Intent to treat	21/408 (5.1%)	25/411 (6.1%)	0.84 (0.48-1.47)	NA	NA
			Late miscarriage or spontaneous Preterm birth < 37 weeks	Subgroup: Singletons	11/395 (2.8%)	12/390 (3.1%)	0.90 (0.40-2.02)	NA	NA
			Late miscarriage or spontaneous Preterm birth < 33 weeks	Subgroup: Singletons	1/395 (0.25%)	5/390 (1.3%)	0.14 (0.02-0.95)	ND	ND
			Mean Gestational length at birth	Subgroup: Singletons	247.6 days	215 days	P=0.02	ND	37
			Mean Birthweight	Subgroup: Singletons	2635 gms	2177 gms	P=0.07	NA	NA
			NICU Admission	Subgroup: Singletons	4/11 (36.4%)	5/10 (50%)	ND	ND	ND
			Mean NICU days	Subgroup: Singletons	18 days	45 days	P=0.14	ND	ND

Treatment	Reference	Gestation al age at treatment	Outcome	Group Analyzed	Number with Outcome/ Number Treated (%)	Number with Outcome/ Number of Controls (%)	Relative risk (95% CI)	Attributable Fraction (95% CI)	Number Needed to Treat
<b>Prior PTB with &amp; without BV</b>									
2% Clindamycin vaginal cream once daily for seven days	Vermeulen, 1999	26 to 32 weeks	PTB	Intent to treat	18/85 (21.2%)	23/83 (27.7%)	1.3 (ND)	NA	NA
			PTB < 34 weeks	Women with BV	1/11(9.1%)	1/11(9.1%)	NS	NA	NA
				Women without BV	(12.5%)	(4.1%)	3.5 (ND) <sup>1</sup>	NA	NA
<b>Abnormal flora (BV plus intermediate)</b>									
2% Clindamycin vaginal cream once daily for three days; plus at 3-4 weeks post treatment- retreatment with seven day course	Lamont, 2003	13 to 20 weeks plus 16 to 23 weeks	Preterm birth		8/208 (4.0%)	19/201 (10.0%)	0.38 (0.16-0.90)	41.7%(-3.4%, 67.2%)	17

<sup>1</sup>The authors also report significantly increased neonatal infectious morbidity among clindamycin treated infants and conclude that prophylactic administration of clindamycin cream to women with normal vaginal flora increases risk for early preterm birth and the risk for serious neonatal infection. (Vermeulen, 1999)