HOW SHOULD BACTERIAL VAGINOSIS BE MANAGED IN PREGNANCY?

Bacterial vaginosis (BV) results from an imbalance in the vaginal bacterial flora (particularly anaerobic bacteria, e.g. *Gardnerella vaginalis* & *Atobopium vaginae*).[1] It is not inflammatory & should not be confused with *vaginitis* associated to parasitic *Trichomonas vaginalis*.[1,2,3] Self-diagnosis is unreliable, even with previous BV history.[1] In Canada, BV prevalence is 14% in pregnancy.[4] 50-75% of women with BV are asymptomatic.[1]

WHAT OBSTETRIC & GYNAECOLOGICAL COMPLICATIONS ARE ASSOCIATED WITH BV IN PREGNANCY? [1,4]

- BV is linked to threatened preterm labour (TPTL) & preterm delivery (PTD), preterm premature rupture of membranes (PPROM), spontaneous abortions, chorioamnionitis, post-partum endometritis, post-Cesarean delivery wound infections, post-surgical infections, & subclinicial pelvic inflammatory disease. PTD likely due to chorioamnionitis is the primary concern in pregnancies with BV (OR 2.19, 95% CI 1.53-3.12).

SHOULD BV BE SCREENED DURING PREGNANCY? [2,4,5,6,7,8,9,10,11,12]

- **Symptomatic** pregnant women **should be tested** (symptoms include presence of vaginal discharge &/or vaginal "fishy" odour which may be more noticeable after intercourse).
- Routine **screening is not required in low-risk pregnancies**.
- There is a **debate** as to whether routine screening should be performed **in high-risk pregnancies** (e.g. history of TPTL, PTD, PPROM & LBW; maternal weight<50kg; short stature; cervical insufficiency). Canadian[SOGC'08 (Level I-B), PHAC'08,'10] & British[BASHH'12] guidelines suggest asymptomatic high-risk pregnant females be screened for BV, at 12-16 weeks gestation; however, American[ACOG'06,'11,CDC'06,'10,USPSTF'08] & International[IUSTI,WHO'11] guidelines state there is insufficient evidence to suggest for or against routine screening of high-risk patients.

WHO SHOULD BE TREATED FOR BV DURING PREGNANCY? [1,2,4,5,6,7,8,9,13,14,15,16,17]

- Treat all patients with positive BV test results. Treatment of BV during pregnancy eradicates the infection & may ↓ the risk of pregnancy complications.[4,5,9,13,14,15] A Cochrane review (n=5888, 15 studies [metronidazole n=7, clindamycin n=7, amoxicillin n=1]) concluded the following:[15]
  - Treatment of asymptomatic BV prior to 20 weeks gestation ↓ risk of PTD (before 37 weeks) (OR 0.72, 95% CI 0.55-0.95, 5 trials, n= 2387).
  - In females with a history of PTD, treatment of asymptomatic BV between 13-28 weeks of gestation did not ↓ risk of PTD (OR 0.83, 95% CI 0.59-1.17, 5 trials, n=622) but ↓ risk of PPROM (OR 0.14, 95% CI 0.05-0.38) & LBW (OR 0.31, 95% CI 0.13-0.75), 2 trials, n=114.
- The suggested **target window for PTD prevention** is **12-16 weeks.**[5,13,16,17]
- Canadian guidelines[SOGC'08 (Level III-L), PHAC'08,'10] recommend retesting for BV 1 month after treatment to ensure eradication of infection following therapy. However, since this recommendation is based on limited data, some practitioners only retest the patient if she is symptomatic at follow-up, or if it is a high-risk pregnancy. See On-Line Extras for comments on recurrent BV.

HOW SHOULD BV BE TREATED IN PREGNANCY? [1,4,5,7,8,13,14]

- The table below lists recommended drug therapies[SOGC'08, PHAC'08,'10, CDC'06,'10, MUMS'12, BUGS & DRUGS'12, BASHH'12, IUSTI,WHO'11]; the male sexual partner does not require treatment.
- **Low-Risk Pregnancy**: **Oral or vaginal** antibiotics can be used, as both are equally effective for eradicating the infection but vaginal antibiotics are not associated with ↓ BV pregnancy complications.[4]
- **High-Risk Pregnancy: Oral** antibiotics are recommended due to potential benefits[SOGC'08(Level I-B)] (↓ BV pregnancy complications & sub-clinical upper-genital tract infections). Topical antibiotics have been used in 1st & sometimes 2nd trimester due to lower systemic absorption.[1,4,5,7]

TABLE: ANTIBIOTIC TREATMENT REGIMENS FOR BV IN PREGNANCY [SOGC'08, PHAC'08,'10, CDC'06,'10, MUMS'12, BUGS & DRUGS'12, BASHH'12, IUSTI, WHO'11, 17,18,19,20,21,22,23]

Drug & Route of Choice

TREATMENT REGIMEN	POPULATION & ERADICATION OR FAILURE RATES	OBSTRETIC COMPLICATION RATES	COST
Metronidazole FLAGYL, g 500mg po BID x 7 days 250mg tablet, 500mg capsule	**Pregnant:** eradication rates of 71% po **vs.** 70% metronidazole 0.75% pv, NS.[18] **Nonpregnant:** eradication rates of 84% po **vs.** 75% metro pv **vs.** 86% clindamycin 2% pv, NS.[19]	Not studied	$9 tabs - $18caps
Metronidazole FLAGYL, g 250mg po TID x 7 days 250mg tablet P_1,$P_{2,3}$ L	**Pregnant:** eradication rates of 70% when metronidazole 250mg po TID for 7 days was combined with erythromycin 333mg po TID for 14 days **vs.** placebo, p<0.001.[20]	**In high-risk pregnancies (i.e.history of PTD or weight <50kg):** • Metro 250mg po TID x 7 days + erythromycin 333mg po TID x 14 days **vs.** placebo, mean gestational age 22.9 wks (22-24 wks):[20] - PTD (<37 wks): metro+eryth 31% vs. placebo 49%, p=0.006, NNT=6. • Metronidazole 250mg po TID **vs.** placebo, at 13-20 wks gestation:[17] - LBW (<2.5 kg): metro 14% vs. placebo 33%, p<0.05, NNT=5. - PTD (<37 weeks): metro 18% vs. placebo 39%, p<0.05, NNT=5. - TPTL: metro 27% vs. placebo 78%, p<0.05, NNT=2. - PPROM: metro 5% vs. placebo 33%, p<0.05, NNT=4.	$9
Metronidazole NIDAGEL 0.75% gel 5gm (= 1 applicator full) pv HS x 5 days 30,45,60,70 gm	**Pregnant:** eradication rates of 70% **vs.** 71% metronidazole 500mg po BID, NS.[18] **Nonpregnant:** erradication rates of 75% **vs.** 84% metro 500mg po BID **vs.** 86% clinda 2% pv, NS.[19]	Not studied	$15-25
P L **Clindamycin* DALACIN C, g** 300mg po BID x 7 days 150mg, 300mg capsule	**Nonpregnant:** failure rates of 6.1% **vs.** 4% metronidazole 500mg po BID, NS.[21]	In asymptomatic BV or abnormal vaginal flora, clindamycin **vs.** placebo x 5 days, at 12-22 weeks (mean gestational age 15.6 weeks): PTD (24-37 weeks) 4.5% vs. 11.6%, p=0.001, NNT=14.[22]	$22
Clindamycin* **DALACIN vaginal cream** ✗ ▼ 2% cream 5gm (= 1 applicator full) pv HS x 5 days 40 gm tube	**Nonpregnant:** eradication rates of 86% **vs.** 84% metronidazole 500mg po BID **vs.** 0.75% metronidazole pv, NS.[19]	In abnormal vaginal flora, clindamycin **vs.** placebo x 3 days of therapy initially followed with another 7 days if abnormal flora persisted after 3 weeks: PTD 4% vs. 10% placebo, p<0.03, NNT=17.[23]	$42

* Some references recommend clindamycin as an alternative treatment due to its association with pseudomembranous colitis (incidence is very rare).[PHAC'08,'10]

ARE THERE HARMS TO TREATING BV WITH ANTIBIOTICS? [1,4,5,7,18,24,25,26,27]

Although treating BV with antibiotics may provide benefit (i.e. ↓ pregnancy complications), concerns of potential PTD & LBW with antibiotic treatment have been raised. [24,25,26]

- **Metronidazole:**
  - The evidence for treating BV with metronidazole in high-risk females is conflicting. Three RCTs showed fewer PTD (<37 weeks) with treatment,[16,17,20] one showed no benefit,[27] & one showed ↑ risk of PTD & LBW with oral metronidazole.[28]
    - The latter study used metronidazole 400mg po BID x 2 days (treatment repeated in 4 weeks if infection still present, 30%) in patients with a mean gestation age of 19.7 weeks. The authors reported an↑ risk of PTD (<37 weeks) in multigravidae (n=74), high-risk pregnancies (previous mid-trimester abortion or PTD) (PTD 43% metro. vs. 24% placebo, p=0.0231).[28] Birth weights were 2,475gm metronidazole vs. 2,759gm placebo (p=0.0109). Differences in outcomes were NS in primigravidae females. Study limitations include use of low dose & short treatment duration, focus on South-African population (↑ risk of BV & PTD with black ethnicity), small population size, & a lower, more asymptomatic number of participants in the metronidazole group.
  - A 2007 meta-analysis assessed the efficacy & safety of antibiotics macrolides, clindamyin & metronidazole during second trimester for the prevention of adverse obstetrical outcomes.[25] The authors concluded that metronidazole was not associated with changes in the rate of PTD, OR 1.1 (95% CI 0.95-1.29, p=0.21), 8 studies, n=2779. However, there was a higher rate of PTD when metronidazole was the only antibiotic administered, OR 1.31 (95% CI 1.08-1.58, p=0.005), 6 studies, n=2006.
    - Of the 8 metronidazole studies included in the meta-analysis, only 4 were for the treatment of BV.
    - All 4 of the BV studies were also included in USPSTF meta-analysis,[9] which concluded there was too much heterogeneity among the studies involving high-risk females to pool the results.
    - This meta-analysis was considered by the 2008 SOGC BV Guideline Committee which recommends metronidazole,[4] but was also the basis for another document which recommends against the use of metronidazole during pregnancy.[26]
  - A 2012 cohort study (n=2,829) reported no association between PTD, LBW, or congenital anomalies & metronidazole for BV or *Trichomonas* treatment in pregnancy.[29]
  - As noted on page 1, various organizations have concluded different recommendations based on the above trials. Comparison of the trials is difficult due to multiple differences in the trial design, e.g. definition & diagnosis of BV, treatment regimen & duration, timing of screening & treatment, inclusion of both low & high risk patients, inclusion of other infections (e.g. Trichomonas).
  - **Overall, studies show more benefit than harm**.
- **Clindamycin:**
  - Oral clindamycin may ↓ the risk of PTD in BV. Topical clindamycin (2% cream pv daily x 7 days) might ↑ PTD & neonatal infections in high-risk pregnancies (PTD history) at 26-33 weeks of gestation (delivery before 34 weeks: 9% clindamycin vs. 1.4% placebo; & infectious neonatal morbidity: 5/83 clindamycin vs. 0/85 placebo, p<0.05 for both).[1,30] Thus, oral clindamycin is recommended over topical SOGC'08,PHAC'08,'10, CDC'06,10 especially in high-risk pregnancies with BV.

IS METRONIDAZOLE SAFE IN PREGNANCY & BREASTFEEDING? [1,24,28,29,30,31,32]

- **Pregnancy:**
  - Either oral or topical metronidazole for the treatment of BV is suitable during pregnancy.
  - Case reports & cohort studies have questioned 1st trimester safety due to a possible association with cancers, particularly neuroblastoma in infants, & teratogenicity in animals.[24] However, after >40 years of use, there is no evidence that metronidazole ↑ rate of major birth defects above the baseline rate of 2-4%, or that there are any detectable side-effects on the fetuses.[31,32] A cohort study investigating cancer was non-statistically significant; neuroblastoma is also a common tumor in pediatrics, preventing a causal relationship with metronidazole.[24]
- **Breastfeeding:**
  - Safety of topical metronidazole has not been studied during breastfeeding and is unlikely to cause concern. Following vaginal administration, maternal plasma levels are <2% of those after a 500mg oral dose, & are 1% of the maternal peak plasma levels after a 250mg oral dose.
  - **Oral** metronidazole is likely safe in breastfeeding. Although it is excreted up to 20% in the breast milk, there are no reports of adverse events in breastfed infants of mothers who took metronidazole.[24] Anectodal reports of loose stools with IV metronidazole resolved when IV therapy was changed to oral, & a possible association with lactose-intolerance remains to be proven.[33] An ↑ risk of *Candida* colonization reported in infants breastfed by mothers on metronidazole 400mg TID is small & NS (7/24 infants vs. 3/31, p=0.053).[30]
  - A 2gm one-time dose followed by expressing & discarding breast milk for 12-24 hours post-treatment is recommended in some references.[1,24,32] Anecdotally infants may reject milk due to a metallic/bitter taste.[34] Monitor breastfed infants for loose stools, thrush, & feeding problems.

IS CLINDAMYCIN SAFE IN PREGNANCY & BREASTFEEDING? [4,24,31,32]

- **Pregnancy:** Either oral or topical clindamycin is considered safe during pregnancy. Clindamycin has no known teratogenic effects during 1st trimester in humans.[24,35] Although very rare, clindamycin is associated to pseudomembranous colitis.
- **Breastfeeding:** Clindamycin, oral or topical, is compatible with breastfeeding. Topical therapy is unlikely to cause concern for the infant, although 30% of a vaginal dose is absorbed into the mother's blood. Oral clindamycin has been associated with diarrhea, thrush or diaper rash, & rare case reports of antibiotic-associated colitis (bloody stools) in the infant.[24] The latter was associated with high doses of clindamycin (600mg IV q6h) in combination with gentamicin, & disappeared 24 hours after treatment discontinuation. Monitor breastfed infants for loose stools (especially bloody stools) & thrush.

See **On-Line Extras** for How is BV vs. *Trichonomas vaginalis* Diagnosed, What are the Risks Factors for BV, How Should BV be Managed in an HIV-positive Pregnancy, How Should Recurrent BV be Treated, Can Other Products be Used for BV, & Comparison of BV Antibiotic Tx Regimens Recommended by Clinical Guidelines. www.RxFiles.ca

✓=recommended in the guideline **-**=not recommended in the guideline ***X*** = Non-formulary in SK ▼=Covered by NIHB **ACOG**=American Congress of Obstetricians & Gynecologists **BASHH**=British Association for Sexual Health & HIV **BID**=twice daily **BV**=bacterial vaginosis **CI**=confidence interval **clinda**=clindamyin **CDC**=Centers for Disease Control & Prevention **FSRH**=Faculty of Sexual & Reproductive Health Care **g**=generic **gm**=gram **HIV**=human immunodeficiency virus **HS**=at bedtime **IUSTI/WHO**=International Union Against Sexually Transmitted Infections/World Health Organization **IV**=intravenous **LBW**=low birth weight **metro**=metronidazole **NYSDoH**=New York State Department of Health **NNT**=number needed to treat **NS**=non-statistically significant **OR**=odds ratio **PHAC**=Public Health Agency of Canada **po**=by mouth **PPROM**=preterm premature rupture of membrane **PTD**=preterm delivery **pv**=per vagina **RCT**=randomized control trial **SOGC**=Society of Obstetricians & Gynaecologists of Canada **TID**=three times a day **TPTL**=threatened preterm labour **USPSTF**=United States Preventive Services Task Force

RxFiles On-Line Extras: How Should Bacterial Vaginosis be Managed in Pregnancy

How is BV vs. Trichomonas vaginalis diagnosed? [1,3,36]

- Signs & symptoms of BV include a thin & off-white/grey malodorous ("fishy smell") vaginal discharge without dyspareunia; while those of *Trichomonas vaginalis* include a thin & green/yellow malodorous vaginal discharge, vulvovaginal erythema, burning, postcoital bleeding, dyspareunia & 'strawberry' cervix.
- Signs & symptoms alone are not sufficiently sensitive or specific to diagnose either infection.
- BV is diagnosed if the patient is positive for ≥ 3/4 Amsel criteria (homogenous thin grayish-white vaginal discharge, vaginal pH > 4.5, positive whiff-amine test with 10% KOH, & clues cells on saline wet-mount); or if gram stain of vaginal discharge gives a Nugent score of 7/10 or a Hay/Ison grade of 3.
- *Trichomanas vaginalis* is diagnosed based on the presence of trichomonads on a wet mount. Since trichomonads remain motile for 10-20 minutes after sample collection, microscopy may become non-diagnostic if performed outside of this timeframe within the clinic. However, if the sample is placed in a medium & sent for clinical laboratory analysis ~$50/swab, this timeframe extends to 3 hours in the Saskatoon Health Region keep at room temperature. Culture or rapid antigen & nucleic acid amplification tests can also be done if available.

What are the Risk Factors for BV? [37,38,39,40,38]

- Risk factors include douching, smoking, young sexually active women (≤14 years old), racial origin (black), intrauterine device (IUD) contraception, female sex partner, new sex partner, or multiple sex partners. A potentially pregnancy-specific risk factor is vitamin D deficiency.[35] Recommend vitamin D 600-2000 IU/day for all pregnant females regardless of BV history or risk.
- It is unclear if any particular lifestyle intervention prevents BV, but smoking cessation & avoiding douching are encouraged. An observational study suggests consistent condom use may ↓ the risk of developing BV (adjusted OR 0.55, 95% CI 0.35-0.88).[41]

How Should BV be Managed in an HIV-positive Pregnancy? [5,42,43,41,42]

- **Screening** for BV in HIV-positive patients should be performed **during the first prenatal visit** [NYSDoH'09 (Level A-II)]. HIV-positive patients have an ↑ risk of preterm delivery (11.1% vs. 7.5% in the general population).[1,44,45] Confirmed BV should be treated using the same drug therapy as for HIV-negative patients.

How Should Recurrent BV be Treated? [1,2,3,5,34,37]

- BV recurs in 15-50% of women within 1-12 months. It is unclear whether BV recurrence is due to resistance, reinfection &/or recurrence.
- No studies or recommendations were located that specifically addressed treatment of BV recurrence or prophylaxis in pregnancy.
- Recurrence can be treated with the same antibiotic regimen used for the initial episode.[1,36]

Can Other Products be used for BV? [1,46,47,48,49,50,51]

- Douching is a risk factor for BV & is not recommended, especially since it may also be an independent risk factor for preterm birth.
- There is insufficient evidence to recommend the use of antiseptics (e.g. boric acid), disinfectants, acidifying agents, *Lactobacillus* probiotics alone or in combination with antibiotics for treatment of BV.

Table: Comparison of BV Antibiotic Treatment Regimens Recommended in Pregnancy by Clinical Guidelines? [4,5,6,7,8,13,14,52,**]

Recommended treatment regimens & durations vary among the Guidelines (see below Table) due to the variation of treatment regimens & durations used in studies, as well as the different antibiotic strengths commercially available in the represented countries.

Treatment	SOGC'08	PHAC'08,'10	MUMS'12	BUGS & DRUGS'12	BASHH'12	FSRH'12	CDC'06,'10	IUSTI,WHO'11
Metronidazole 500mg po BID x 7 days	✓	✓	✓	✓	-	-	✓	✓
Metronidazole 400mg po BID x 5-7 days	-	-	-	-	✓	✓	-	✓
Metronidazole 250mg TID x 7 days	-	-	-	-	-	-	✓	-
Metronidazole 2gm po as single dose	-	-	-	-	✓	-	-	✓
Metronidazole 0.75% gel 5gm (=1 applicator full) pv HS x 5 days	-	-	✓	-	✓	✓	-	✓
Clindamycin 300mg po BID x 7 days	✓	✓	✓	✓	✓	-	✓	✓
Clindamycin 2% cream 5gm pv HS (=1 applicator full) x 5 days	-	-	✓	-	✓	✓	-	✓

**ACOG: recommended regimens for nonpregnant patients only.

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