



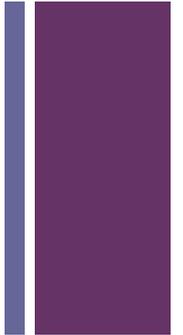
Educational Half Day
3/17/21
Journal Talk

Jolie Cooperman PGY2

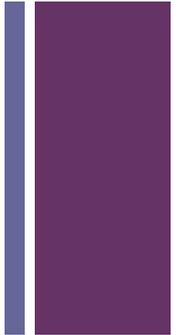
+ Bacterial Vaginosis and its association with infertility, endometritis, and pelvic inflammatory disease

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Expert Review, AJOG Mar 2021



+ Purpose



- Review the current evidence for the associations among BV, PID, and endometritis
- Review the impact of untreated BV and PID on infertility



Introduction



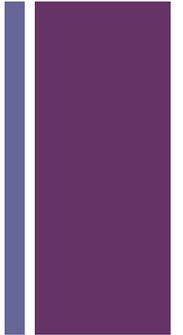
- The vaginal microbiota of healthy, reproductive age women typically include aerobic, facultative anaerobic, and obligate anaerobic species
- Lactobacilli predominates
- Disruption of the predominance of lactobacilli is associated w/ increased risk of STI and upper genital tract infections via ascension of pathogens and other anaerobic bacteria

+ Bacterial Vaginosis



- Affects 29% of women of reproductive age in the US
- Develops via the disruption of vaginal microbiota characteristics due to decreased amounts of lactic acid producing bacteria and increased presence of strict and facultative anaerobes
 - *Gardnerella vaginalis*, *Megasphaera* spp., *Atopobium vaginae*, *Dialister* spp., *Mobiluncus* spp., *Sneathia amnii*, *Sneathia sanguinegens*, *Prophyromonas* spp., and *Prevotella* spp.
- Symptoms: asymptomatic – symptomatic (vaginal odor, itching, discharge)
- Associated w/ serious adverse health outcomes

+ PID & Endometritis



- Upper genital tract infections
- Acute PID: ascension of strict or facultative anaerobes from the vagina to the endometrium and adnexa \leq 30 days
- Chronic endometritis lasts longer than or equal to 30 days
- $>95\%$ PID cases are caused by BV related bacteria and/or STIs



BV: Diagnosis and Treatment



- At least 3 signs and symptoms of the Amsel criteria
- Nugent scoring system
- 2020 ACOG Practice Bulletin on BV in non-pregnant patients recommended PO flagyl, intra-vaginal flagyl gel, or intra-vaginal clinda cream
- Single dose oral secnidazole was approved by US Food and Drug Admin
- Choice of treatment can be individualized given comparable safety and efficacy profiles
- BV is highly recurrent
- No need to treat asymptomatic patients per CDC
- New treatment combinations: *Lactobacillus crispatus* + antimicrobials

+ Amsel Criteria

TABLE 1

Amsel criteria for the diagnosis of BV

1. Homogenous, thin, grayish-white vaginal discharge that smoothly coats the vaginal walls
2. Presence of $\geq 20\%$ clue cells on saline wet mount
3. Vaginal pH of >4.5
4. Positive whiff-amine test result

BV, bacterial vaginosis.

*Ravel. Bacterial vaginosis and association with infertility, endometritis, and pelvic inflammatory disease. Am J Obstet Gynecol 2021.*²²

+ Treatment



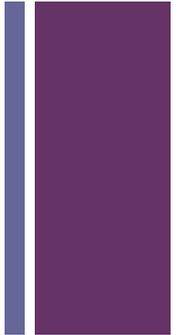
TABLE 2
ACOG treatment recommendations for the management of BV in nonpregnant patients

Drug	Formulation	Dosage	Duration
Recommended treatment regimens			
Metronidazole	Oral	500 mg, twice daily	7 d
Metronidazole	Intravaginal gel 0.75%	5 g, once daily	5 d
Clindamycin	Intravaginal cream 2%	5 g, once daily at bedtime	7 d
Alternative treatment regimens			
Secnidazole	Oral	2 g, single dose	1 d
Tinidazole	Oral	2 g, once daily	2 d
Tinidazole	Oral	1 g, once daily	5 d
Clindamycin	Oral	300 mg, twice daily	7 d
Clindamycin	Intravaginal ovules	100 mg, once daily at bedtime	3 d

ACOG, American College of Obstetricians and Gynecologists; BV, bacterial vaginosis.

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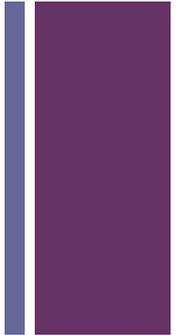
+ BV and Fertility



- Linked specifically to tubal infertility
- In a study of women undergoing oocyte recovery for IVF, seropositivity for Chlamydia species and presence of BV were both strongly and INDEPENDENTLY associated with tubal infertility
- In a sample of patients seeking fertility treatment, Nugent-BV was present in 31.5% of patients w/ tubal infertility and 19.7% of patients with nontubal infertility
- Idiopathic infertility has been linked to a unique vaginal bacterial signature that includes bacteria related to BV
- In a systematic and metaanalysis review...
 - Looking at BV and fertility: BV was 3.3x more likely to be identified in infertile women than in antenatal women within the same population
 - Looking at BV and IVF treatment: 16% prevalence of BV was observed
- Women with a lower prevalence of vaginal lactobacilli were less likely to have successful embryo implantation

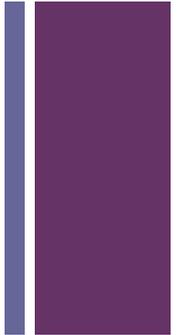
+ Ultimately...

There is a clear association between BV and infertility,
causality has not been conclusively determined





BV and Infertility: Mechanisms



■ Inflammation

- Higher levels of cervical cytokines reported in women w/ BV and infertility
- Probiotic vaginal tablets to correct imbalances in microbiota are being studied > reduces cytokine levels

■ Sialidase and other mucinases affecting cervical mucus integrity

■ Increasing risk for acquiring STIs

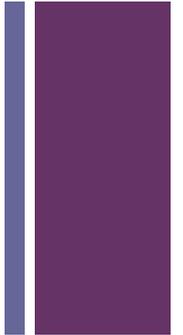
- Chlamydia: 3.4x
- Gonorrhea: 4.1x
- Trichomonas, HSV, HIV, HPV

■ Increasing risk for upper genital tract infection and PID

- Women w/ acute endometritis were 90% less likely to have typical ratios lactobacilli and were 2.4x more likely to have Nugent-BV
- Subclinical PID is 2.7x more common in patients w/ Nugent-BV



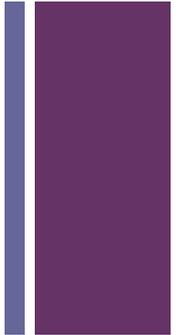
Endometritis and PID: Fertility



- Presence of BV associated bacteria in the endometrium has been linked to a 3.4 fold increased risk of fertility
- In a study of women w/ Nugent-BV, gonorrhea or chlamydia or at risk of infections, such as gonorrhea or chlamydia, researchers prospectively evaluated pregnancy outcomes after a biopsy was performed to identify endometritis. Participants were treated for BV and other infections. After a median of 2.1 years of follow up, women with subclinical PID at diagnosis had a 40% decreased likelihood of pregnancy compared with those without subclinical PID
- Large population-based study: Tubal infertility was found in 10.8% of patients diagnosed w/ PID compared to 0% of those who tested negative
- Infertility was reported by 24.2% of women with past history of PID treatment compared with 13.3% of women without PID treatment
- CE is highly prevalent among patients with unexpected fertility at 33-66%
- Although lower prevalence of lactobacilli have been associated w/ BV and endometritis, there is no standard definition of abnormal and normal endometrial microbiota and the abundance of these bacteria in the endometrium is unknown
- Women with cured CE compared with those with persistent CE had a lower pregnancy rate and lower live birth rate after IVF



Managing BV, PID, and Endometritis Before Pregnancy



- A low level of clinical suspicion for BV, CE or PID should be sufficient for initiating testing in women w/ risk factors for these infections, such as a history of STIs or sexual behaviors that could lead to transmission
 - Particularly true for women suffering from infertility or tubal infertility
- Treatment of genital infections may improve fertility outcomes
 - results in significantly higher pregnancy rate
 - In women undergoing IVF, those w/ cured CE had a 6.8 fold higher ongoing pregnancy and live birth rate and a 4 fold higher clinical pregnancy rate than those with persistent disease
 - Effects of performing IVF w/ Lactobacillus colonized on catheter tip is being studied
- Treatment is for symptomatic women



Take Home Points



- BV isn't a benign infection
- BV, endometritis, PID and infertility are related to interconnected pathophysiological pathways
- Several mechanisms for this relationship have been proposed: inflammation, immunity, microbiota, etc
- Additional large, prospective, longitudinal studies are needed to conclusively link
- Asymptomatic BV?



Thank you!