

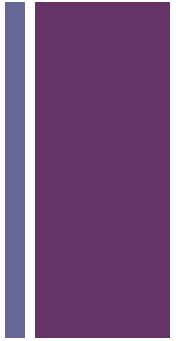
**Educational Half Day**  
**3/17/21**  
**Journal Talk**

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# + 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

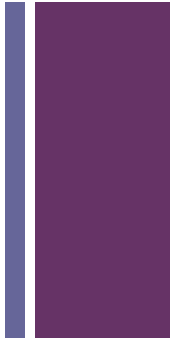


# Introduction



- 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.*<sup>22</sup>



# + Treatment

**TABLE 2**

**ACOG treatment recommendations for the management of BV in nonpregnant patients**

| <b>Drug</b>                    | <b>Formulation</b>     | <b>Dosage</b>                 | <b>Duration</b> |
|--------------------------------|------------------------|-------------------------------|-----------------|
| 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.

Ravel. Bacterial vaginosis associated with infertility, endometritis, and pelvic inflammatory disease. *Am J Obstet Gynecol* 2021.<sup>22</sup>

# + 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!