Educational Half Day
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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., atopbium 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 ≤ 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.

### TABLE 2

ACOG treatment recommendations for the management of BV in nonpregnant patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended treatment regimens</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Oral</td>
<td>500 mg, twice daily</td>
<td>7 d</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Intravaginal gel 0.75%</td>
<td>5 g, once daily</td>
<td>5 d</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Intravaginal cream 2%</td>
<td>5 g, once daily at bedtime</td>
<td>7 d</td>
</tr>
<tr>
<td><strong>Alternative treatment regimens</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secnidazole</td>
<td>Oral</td>
<td>2 g, single dose</td>
<td>1 d</td>
</tr>
<tr>
<td>Tinidazole</td>
<td>Oral</td>
<td>2 g, once daily</td>
<td>2 d</td>
</tr>
<tr>
<td>Tinidazole</td>
<td>Oral</td>
<td>1 g, once daily</td>
<td>5 d</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Oral</td>
<td>300 mg, twice daily</td>
<td>7 d</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Intravaginal ovules</td>
<td>100 mg, once daily at bedtime</td>
<td>3 d</td>
</tr>
</tbody>
</table>

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

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 with 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 endometirtis 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 with 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 with 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 with 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!