Hormonal contraception is associated with stability and Lactobacillus-dominance of the vaginal microbiota in a two-year observational study


How would HC reduce BV?

- HC, especially those containing progestins, inhibit uterine bleeding and reduce menstrual loss. Menses ~ abnormal vaginal microbiota.
- Adequate estrogen levels increase glycogen production in vaginal epithelial cells, and glycogen is broken down into metabolites used by Lactobacillus spp. to thrive and produce lactic acid.
- HC may also promote a favorable anti-inflammatory cytokine milieu that facilitates BV clearance.
- Despite >50 years of widespread use, the effect of HC on the vaginal microbiota are still incompletely understood and have not been widely studied.

Methods

- The study is ongoing.
- To date, we have analyzed 112 women (>2,800 mid-vaginal samples).
- This analysis is based on the three most commonly chosen HC methods: oral contraceptive pill (OCP), vaginal ring, implanton.
- Controls not taking HC were also followed.
- Microbiota analysis:
  - Vaginal microbiota composition was characterized by 16S rRNA gene analysis of the V3-V4 hypervariable regions.
  - We identified community state types (CSTs) which are categories based on the diversity and relative abundance of taxa detected.
  - A multinomial model for dependence of proportions was used to evaluate the association between CST and HC.
  - Jensen-Shannon distances between all pairs of samples were analyzed to assess stability of the microbiota longitudinally.

Hormonal contraceptives (HC) and bacterial vaginosis (BV)

- With BV ~ STIs and treatments for BV sub-optimal, any additions to the BV treatment toolkit are welcomed.
- The data suggest that HC use, particularly OCP, DMPA and implants, are associated with decreased BV recurrence in some women.
  - Data are sparse on how intrauterine devices (copper & hormonal) and contraceptive vaginal rings affect the vaginal microbiota.
- HC use is common.
  - 17% of U.S. women aged 15-44 years (~18 million) use HC.
- Why does HC use decrease the risk of BV recurrence in some women but not others?
  - We sought to determine how HC use affects the vaginal microbiota in an observational cohort.

Study Population

- 16 to 35 year old women initiating or planning to discontinue HC (mean 26 years).
- 64% white and 25% African American.
- Age-matched control women presenting for routine gynecological care who were not interested in starting HC.
- Time from last HC use has been at least 3 months for OCP and 6 months for the longer acting formulations (e.g. DMPA).
- All women initiating HC undergo clinical evaluation to ensure safety, and to determine the most appropriate HC formulation.
- Exclusion criteria included: any contraindications to HC, hysterectomy, known condition altering sex hormone cycles (e.g. polycystic ovarian syndrome, premature-ovarian failure, etc.), known immunodeficiency, diabetes mellitus, contraindications for HC use (also applied to the control group).

Study design - HCL

- Visits were scheduled at baseline, 2 weeks, 4 weeks, 3 months, 6 months, 12 months, 18 months, and 24 months.
- Additionally, participants self-collected mid-vaginal swabs twice-weekly in the two weeks before each visit.
- Daily behavioral diary collected in 2 weeks before each visit.
- Blood, urine, vaginal swabs collected.
- STI screening at baseline and follow-up as necessary.
Stability of the vaginal microbiota

- Women on OCPs had more stable bacterial communities than controls during the 2-year follow-up (p=0.04).
- HC (overall) also tended toward greater stability (p=0.10).

Association between hormonal contraception and community state type (CST)\(^1\) compared to women on no HC in a longitudinal study

<table>
<thead>
<tr>
<th>CST</th>
<th>dominant bacteria</th>
<th>OCP(^1)</th>
<th>Ring</th>
<th>Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>L. crispatus</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>II</td>
<td>L. iners</td>
<td>+</td>
<td></td>
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<tr>
<td>IV-A*</td>
<td>Low-Lactobacillus</td>
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<td>0</td>
<td></td>
</tr>
<tr>
<td>IV-B*</td>
<td>Low-Lactobacillus</td>
<td>-</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>L. amnalis</td>
<td>+</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) CSTs reflect the clustering of samples based on bacterial composition and abundance.

\(^*\) CST IV-A is characterized by various species of anaerobic bacteria including Anaerococcus, Peptostreptococcus and Prevotella spp., whereas CST IV-B had higher proportions of bacteria from the genera Gardnerella, Atopobium and Megasphaera among others.

\(^\d\) The “*” is increased, “” is decreased and 0 is not statistically significant.

Change in CST over time with OCP initiation

Proportion of CSTs for women initiating OCP, n=11 women and 385 observations
Difficulties in HC studies

- Overall, where data on HC and BV are conflicting, it is most likely due to a number of factors including:
  - heterogeneity of approaches used to diagnose BV and assess vaginal microbiota
  - observational nature of the studies:
    - sexual behaviors, and particularly condom usage, may change with HC
    - regimen compliance
    - switching of HC types
    - the availability of various formulations of HC with differences in progestational activity