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Live biotherapeutics for preterm birth prevention: vaginal administration of *Lactobacillus crispatus* CTV-05 in pregnancy leads to persistent colonisation and reduces inflammation

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Background

A vaginal microbiota colonised by *L. crispatus* (Community State Type; CST1) is protective against preterm birth (PTB).[1]

Both *L. iners* (CST3) and *Lactobacillus* deplete, high diversity communities (CST4) associate with increased risk.[2]

Objectives

We determined whether a live vaginal biotherapeutic containing *L. crispatus* CTV-05 (LACTIN-V) (2x 10^9 CFU) colonises the vagina and reduces local inflammation in pregnancy.

Methods

LACTIN-V (fig 1) was administered once daily for five days from 14 weeks of pregnancy, and then once weekly for six weeks to 62 women at high-risk of PTB. At each timepoint (T) vaginal swabs were collected (fig 2). Vaginal microbiota was assessed using metataxonomics.

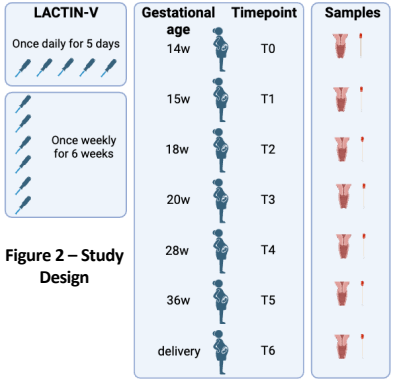


Figure 2 – Study Design

Figure 1 – LACTIN-V pre-filled applicator

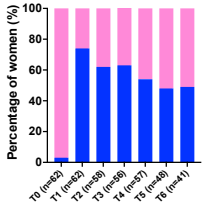
Colonisation was determined by quantitative PCR (qPCR) and a CTV-05 specific amplicon sequence variant (ASV-02). Pro-inflammatory cytokines were measured from cervicovaginal fluid (CVF) using immunoassays at T0, T1, T3 and T4. Statistics were done by one-way ANOVA Kruskal-Wallis and Dunn's correction.

Results

1. LACTIN-V detection

Detection, defined as presence of the CTV-05 specific ASV-02, increased with usage and was maintained for most participants (fig 3).

Figure 3 – LACTIN-V detection



2. LACTIN-V colonisation

Colonisation, defined as ASV-02 presence at 28 weeks of pregnancy, was seen in 54% (31/57) of women. Similar results were seen with qPCR. Colonisers were less likely to have pre-treatment CST1 (p<0.0002), and more likely to have CST3 or 4 (p=0.0179).

3. CST shifts

Pre-treatment, 43% of women had CST1, increasing to 89% and 87% at 8- and 16-weeks post-treatment (p <0.0001) (fig 4).

4. Cytokine concentrations

Cytokine concentrations reduced throughout the study for IL-1β and IL-8 (fig 5 & 6). IL-6 detectability reduced across the study (fig 7).

Figure 5 - IL-1β with LACTIN-V

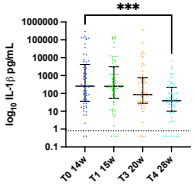


Figure 4 – CST shifts

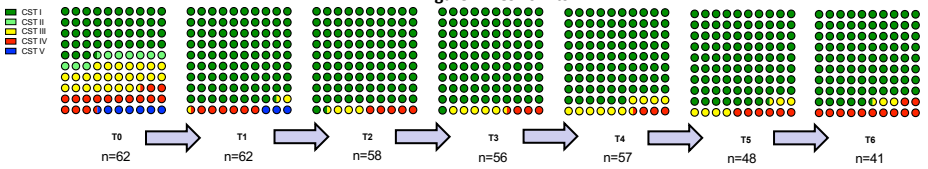


Figure 6 - IL-8 with LACTIN-V

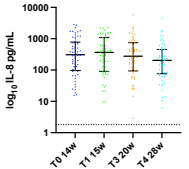
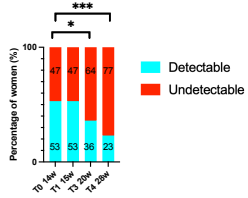


Figure 7 - IL-6 detectability



Comparisons of concentrations at T0 versus T4 showed a reduction for IL-1β (p=0.0002) (fig 5) and IL-8 (p=0.2384) (fig 6). IL-6 detectability also reduced (p=0.0003) by T4 (fig 7).

Conclusion

LACTIN-V induces persistent colonisation, displacing less favourable bacteria in women whose vaginal microbiota is initially dominated by *L. iners* or is highly diverse (CST4). This associates with reduced cytokine concentrations. LACTIN-V causes modulation of the microbiota and the immune milieu to a protective state and could reduce PTB risk.

References

1. Kindinger, L.M., et al., 2017. The interaction between vaginal microbiota, cervical length, and vaginal progesterone treatment for preterm birth risk. *Microbiome*, *5*, pp.1-14.
2. Brown, R.G.,et al., 2019. Establishment of vaginal microbiota composition in early pregnancy and its association with subsequent preterm prelabor rupture of the fetal membranes. *Translational Research*, *207*, pp.30-43.