

# Final report form

**Date of sending out the form:**

Monday, June 3, 2019

**Contact person/applicant:**

Amy Matser

**Country**

NL

**E-mail**

amatser@ggd.amsterdam.nl

**Title of the granted project**

The relationship between the use of hormonal contraceptives, the composition of the vaginal microbiota, and the risk to acquire Chlamydia infection among women

**Amount granted by the ESC (in euro)**

9420

**Project number:**

P-2016-B-03

**Allocated mentor:**

P Baraitser

**Date project actually started:**

Wednesday, February 1, 2017

**Date of completion:**

Friday, March 15, 2019

**Please provide a report of your findings and data.**

Results 1. The relationship between hormonal contraceptive (HC) use and STI among 50,278 women at the STI outpatient clinic of the public health service of Amsterdam

We used data from 50,278 women during 87,153 consultations between January 2009 and October 2016. Logistic regression analyses using generalized estimating equations were used to

assess the association between HC use and Chlamydia or gonorrhea infection. The analysis was stratified by visiting reason: 1) STI-related symptoms, 2) partner notification, 3) sex worker, 4) other reasons (defined as low-risk women). In multivariable analyses, we accounted for age, ethnicity, the number of partners in the preceding 6 months, and condom use with steady and casual partners. Data on condom use was not available for women in the 'other' category. In the Chlamydia analysis, we also accounted for gonorrhea diagnosis, as marker of high-risk sexual behavior.

The mean age of the participants was 24 (sd 5.4) and 73% had a Dutch ethnic background. Non-genital tract HC (non-GT-HC) use was reported during 17,232 (59.2%) clinic visits, vaginal ring (VR) use during 743 (2.6%) visits, hormonal intra-uterine device (hIUS) use during 1,031 (3.5%) visits, and no use during 10,105 (34.7%). Inconsistent condom use with a casual partner in the preceding 6 months was reported by 31.8% of non-HC users, 34.8% of the non-GT-HC users and by 18.5% of VR or hIUS users.

Chlamydia. Among low-risk women (n=48425), Chlamydia was diagnosed in 5.3% of the 14,457 consultations by women who did not use HC and in 6.1% of women who used non-GT-HC in 31,374 consultations. In 3.1% of the 1,405 visits by VR users Chlamydia was found, and in 9.1% of 1,189 visits by hIUS users. In multivariable analyses, the adjusted odds ratio (aOR) for being diagnosed with Chlamydia was 1.17 (95% CI 1.07-1.27) for non-GT-HC users, 0.58 (95% CI 0.42-0.79) for VR users, and 1.78 (95% CI 1.43-2.22) for hIUS users, compared non-HC users.

Among visits by women with STI-related symptoms or partner notification (n=29,111), the Chlamydia positivity rate was 18.1% when non-use was reported, 27.1% when non-GT-HC was reported, 22.1% when VR use was reported, and 12.9% when hIUS was reported. Among women with STI-related symptoms, only non-GT-HC was significantly associated with Chlamydia positivity (aOR 1.18 [95% CI 1.06-1.32]), while VR or hIUS were not significantly associated. Among women who were notified, the aORs were 1.50 (95% CI 1.33-1.69) for non-GT-HC use, 1.52 (95% CI 1.11-2.09) for VR use, and 0.76 (95% CI 0.60-0.97) for hIUS use.

Among sex workers, non-GT-HC use was reported

during 3,607 (37.5%) clinic visits, VR use during 88 (0.9%) visits, hIUS use during 98 (1.0%) visits, and no use during 5,824 (60.6%) visits. Sex workers were significantly older than women in the other groups ( $p < 0.001$ ). 78.7% of women reported >100 partners in the preceding 6 months. The majority of women reported a steady partner without condom use or inconsistent use. Inconsistent condom use with casual partners was reported by 33.4% of non-HC users, 31.5% of non-GT-HC users, 25.0% of VR users, and by 35.1% of hIUS users. Chlamydia positive rates were 5.2%, 6.0%, 3.4%, and 8.2%, respectively. The aOR for non-GT HC use was 1.13 (95% CI 0.93-1.47), 0.74 (95% CI 0.22-2.57) for VR use, and 1.37 (95% CI 0.64-2.93) for hIUS use.

**Gonorrhea.** Gonorrhea was rare among women visiting the STI clinic in Amsterdam. It was diagnosed in 91 (0.7%) clinic visits by non-HC using women, in 102 (0.4%) visits by non-GT-HC using women, in 3 (0.2%) visits by VR using women, and in 8 (0.7%) visits by hIUS using women. In multivariable analysis, low-risk non-GT-HC women using women were less likely to be diagnosed with gonorrhea than non-using women (aOR 0.66 [95% CI 0.48-0.90]), while the gonorrhea risk of VR and hIUS use did not differ significantly from the non-using risk. Among women who had STI-related symptoms or were notified, non-GT-HC, VR, and hIUS use all significantly lowered the odds of being diagnosed with gonorrhea, compared to non-using women (aOR 0.63 [0.53-0.74], aOR 0.35 [95% CI 0.16-0.78], and aOR 0.24 [0.10-0.53], respectively). Contraception use was not significantly associated with gonorrhea diagnosis among sex workers. In general, the risk to be diagnosed with gonorrhea was lower among women using HC, compared to women who did not use HC.

**Sub-analysis.** A sub-analysis on women who visited the STI clinic in 2010 and participated in a scientific study on sexual network (the Hetero Networkstudy) did not provide any further evidence. Among 983 women with a median age of 24 (IQR 22-28), the Chlamydia positivity rate was 13%. Non-GT-HC use was reported by 517 women of whom 71 (13.7%) had Chlamydia. Among 312 non-users, the Chlamydia positivity rate was 13.1%. Among hIUS users ( $n=109$ ) and VR users ( $n=35$ ), the positivity rates were 11.0% and 8.6%, respectively. The OR being infected with Chlamydia

a was 1.04 (95%CI 0.82-1.32) among women using Non-GT-HC and 0.75 (95% CI 0.51-1.10) for women using hIUS.

In total, 24 women tested positive for gonorrhoea of whom 13 did not use hormonal contraception and 8 used non-GT-HC. The OR being infected with gonorrhoea was 0.28 (95%CI 0.17-0.48) among women using non-GT-HC.

Results 2. Effects of an over-the-counter lactic-acid containing intra-vaginal douching product on the vaginal microbiota

Background. Over-the-counter intra-vaginal lactic-acid containing douches are marketed as vaginal hygiene products that support optimal vaginal pH balance. We report the effect of a commercially available douche (Etos®) on the vaginal microbiota (VM) in a prospective study.

Methods. Healthy women, aged 18-36 years, were recruited in 2015-2017 (ethical approval: METC-2014\_413). Participants were followed over three menstrual cycles and were instructed to douche three times during the second cycle, starting on the first day of that cycle. Participants completed a questionnaire at baseline, kept a daily diary to report douching, menses and sexual activity, self-collected vaginal swabs every other day during the first and third cycle and daily during the second cycle, and measured vaginal pH mid-cycle. A median of 44 vaginal swabs [inter-quartile range (IQR): 41-50] were assessed per participant by 16S rRNA gene (V3-V4 region) sequencing and a *Candida albicans* PCR was done at four time-points.

Results. The included 25 participants had a median age of 24 years [IQR: 22-29], were mostly Dutch-Caucasian (88%), and 60% used combined oral contraceptives. At baseline, 21 participants (84%) had Lactobacillus-dominated VM (*Lactobacillus crispatus* (n=14), *L. iners* (n=6), or diverse *Lactobacillus* species (n=1)) and 4 participants (16%) had VM consisting of diverse anaerobes. In multinomial logistic regression models, increased odds were observed for having diverse anaerobic VM in the second and third cycle, compared to the first cycle, after adjusting for menses, although non-significantly (odds ratio (OR)=1.4 (95% CI: 0.9-2.1) and OR=1.7 (95% CI: 0.9-3.1), respectively) (p=0.376). Douching did not affect vaginal pH. Menses increased the odds for having

VM consisting of diverse anaerobes almost two-fold (OR=1.7; 95% CI: 1.0-2.8), while douching during menses increased the odds 2.6 fold (OR=2.6; 95% CI: 1.0-6.5), compared to not menstruating (p=0.099). Participants were more likely to test positive for *C. albicans* after cycle 2, compared to cycle 1 (OR = 3.0 (95% CI: 1.2 – 7.2); p=0.017).

**Conclusion.** The Etos® douche did not significantly affect the vaginal pH or VM composition, although increased odds for having diverse anaerobic VM was observed, especially when douching during menses. Furthermore, douching may promote *C. albicans* infections.

**Overall discussion.** In general, we found that the Chlamydia risk was slightly higher among women using non-genital tract hormonal contraceptives (e.g. oral pills) as compared to women who did not use hormonal contraceptives. Hormonal contraceptive use seems to lower the odds of acquiring gonorrhoea infection. Results should be interpreted with caution, because it is very likely that there is residual confounding caused by limited sexual risk behavior data. Mixed results are in line with current literature on this topic. Furthermore, we found that the vaginal microbiota is negatively affected by menses. This suggests that hormonal contraceptive methods that neutralize or stop the menstrual cycle may contribute to a more stable and healthy vaginal microbiota, and subsequently lower the risk of acquiring STI.

**Please provide a final detailed budget on how much you have spent. Was any money not spent? Receipts may be requested.**

The money was spend to cover the salary costs of the postdoctoral researcher (A. Matser) to work on women's health related to the hormonal contraceptive use, vaginal microbiota, and sexually transmitted infections.

4793,- Supervising (PhD-)students performing the analyses (65 hours)

5138,- Analyzing and drafting manuscripts (72 hours)

2675,- Acquisition (37 hours)

12606,- Total

9420,- Grant

3186- Own expenses

### How will your findings be presented?

Publication in journal

Presentation

### Was your paper published? Indicate journal and acceptance date

Van der Veer C, et al. Effects of an over-the-counter lactic-acid containing intra-vaginal douching product on the vaginal microbiota [In submission phase, expected to be published in a microbiology journal in 2019]

A. Matser, et al. The relationship between hormonal contraceptive (HC) use and STI among 50,278 women at the STI outpatient clinic of the public health service of Amsterdam [Finalizing draft, expected to be published in a women's health/STI journal in 2019]

### Presentation – note meeting organisation and date

Presentation of results during the ESC conferences, Dublin, 2020

### Add any other information you feel we should have

I want to apologize for the poor communication during this project. Two years ago, the initial plan was to start my own research line focusing on vaginal health (hormonal contraceptive use, vaginal microbiota and sexually transmitted infections). I have learned that it is a difficult to get research funding for this topic, but I am still committed to proceed. I am very grateful that I have received your grant to start the research line.

### Please let us know whether having a mentor has been helpful or not

I am not used to having a mentor from a grant provider. For us, a department where scientific research is routine, the added value of a mentor is limited, because the knowlegde about how to perform research is available.

### Full Name

Antoinette Amy Matser

**Date**

Monday, June 3, 2019

Questions? ESC Central Office: [info@escrh.eu](mailto:info@escrh.eu)

**Type a question**

info@escrh.eu