# The effect of medical grade honey (L-Mesitran) for cervical intraepithelial neoplasia-II

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The primary aim of this study is to investigate the effect of honey on the clearance of the hr-HPV virus in patients with CIN II.Secondary, the effect of honey on the normalization of CIN lesions, the role of the vaginal microbiome, the local immune...

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Other condition |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON56731

**Source**
ToetsingOnline

**Brief title**
Honey for CIN-II

### Condition

- Other condition
- Viral infectious disorders
- Reproductive neoplasms female malignant and unspecified

**Synonym**
cervical dysplasia, pre-cancerous cervical cells

**Health condition**

Pre-maligne cervix afwijkingen, CIN II

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** Zuyderland Medisch Centrum
**Source(s) of monetary or material Support:** Research en Innovatie subsidie van het Zuyderland MC,Triticum Exploitatie BV

## Intervention

**Keyword:** CIN-II, Honey, HPV, Microbioma

## Outcome measures

### Primary outcome

Clearance of hr-HPV at 6 months.

### Secondary outcome

Secondary outcome measure:

- Regression of CIN II defined as a regression to Pap1

- Clearance of hr-HPV and normalization of cytology (KOPAC) at 12-24 months

(depending on NVOG/RIVM flowchart). Histology as in regular care.

- Characteristics of the vaginal microbiome; species specific and diversity

analysis (T:0 and T:6 months), changes due to honey and relationship with the

other outcome measures.

- Cervical immune status; immunohistochemical stains (T:0) for T and Myeloid

cells (CD4, CD11c, CD168, CD68 and Foxp3). These markers have been used in

similar studies of imiquimod in CIN and vulvar HPV lesions.

- Human vaginal gene expression profiles (including mRNA inflammatory markers)

(T:0 and T:6 months).

- Quality of life, side-effects and compliance with the honey.

# Study description

### Background summary

Cervical cancer is caused by the high-risk human papillomavirus (hr-HPV). 80% of sexually active women get infected by hr-HPV during their lifetime, 10% persists and 0.6% develops cervical cancer. This development proceeds gradually through precursor lesions (CIN I, II and III). The standard treatment for CIN II/III is a large loop excision of the cervix(LLETZ). In young women with a (future) desire to have children, a LLETZ can lead to an increased risk of premature birth and fertility disorders. An alternative is an immunomodulatory cream (Imiquimod), unfortunately, 45% of patients do not respond to the treatment, in addition, there is a 10% dropout due to side effects.

With CIN II, the chance of spontaneous regression is +/- 55%, so the advice for young women is to wait and see. However, the other half persists or progresses to CIN III and the often lengthy follow-up can lead to anxiety and worry.
Patients with CIN II benefit from non-invasive treatments with minimal side effects. It is known that both the immune system and the vaginal microbiota play an important role in the clearance of HPV. Medical grade honey has the potential to act on these defense mechanisms of the body to help clear hr-HPV and CIN II. Firstly, medical grade honey positively influences the vaginal microbiome through its favorable acidity, the release of hydrogen peroxide, reducing pathogenic bacteria, and the promotion of Lactobacilli. Secondly, medical grade honey has immunomodulatory and anti-inflammatory activity. Moreover in vitro studies and pre-liminary human cohort studies show a direct antiviral activity. This suggests that honey may be able to modulate the microenvironment to clear the hr-HPV and precursor lesions.
This is the first study using honey to treat CIN. The potential impact is fewer additional treatments 1and a quicker resolution of HPV, necessitating less aftercare thereby reducing stress and costs. Moreover, due to a decrease in invasive treatments (less LLETZ), we expect a long-term effect on the care burden due to a decrease pregnancy related complications such as preterm rupture of membrane and preterm births

### Study objective

The primary aim of this study is to investigate the effect of honey on the clearance of the hr-HPV virus in patients with CIN II.
Secondary, the effect of honey on the normalization of CIN lesions, the role of the vaginal microbiome, the local immune system and the intravaginal inflammatory status is investigated.

### Study design

In this pilot study, we will include 60 patients with newly diagnosed CIN II. Patients will be counseled according to standard guidelines between a LLETZ, imiquimod or expectant management. Patients choosing for expectant management will be asked to participate in the study for the intervention cohort with medical grade honey. Expectant managment patients who choose not to participate in the intervention cohort are ask for the control cohort of the study (observational cohort with regular standard care). Follow-up assessment takes place in accordance with the national guideline (first check-up is after 6 months). In addition, swabs for vaginal microbiota analysis will be taken at 0 and 6 months. Immunohistochemical stainings for the local immune infiltrate will be performed on biopsies taken during regular colposcopy at t=0. At the start of treatment, 6,12 and 24 months two questionaires regardings side-effects and quality of life will be sent to the patient.
This exploratory study assesses the potential effect of honey, the optimal dosage and provides insight into its mechanisms of action.

**Intervention**

Medical grade honey formulation (MGH) (L-Mesitran®) for CIN II
Daily application of 5 grams (with applicator) for 3 months. Then weekly applications (5 grams with applicator) for 3 months.

**Study burden and risks**

Only one extra visit is needed for participation in the study (explanation of L-Mesitran treatment and delivery of L-Mesitran) . In order to investigate the effect of MGH on microbiological and vaginal gene expression levels at the start of the study and 6 months, vaginal swabs will be collected at these time points. To minimize the burden on the patients, patients will be asked to take a vaginal swab themselves using a self-test at the start of the study or the researcher will perform them if requested during the starting visit, the swabs and PAP smear after 6 months can be collected during the regular visit. The swabs will be sent by pre-paid mail to the MUMC were they will be stored for analysis. In addition, patients will be asked to fill in 2 questionnaires at inclusion, and 6, 12 and 24 months after the start of L-Mesitran. The questionnaires will be sent digitally. To check for adherence and side-effects we ask the participants to fill in a weekly journal.
The investigational product L-Mesitran® is registered for the treatment of wounds and has CE certification and FDA approval. No contraindications are known to date. It is advised not to use the product on patients who are sensitive to the product or any of its components or patients with an allergy to honey, which is very rare and only very few cases have been reported. Based on previous studies investigating the activity of honey for the beneficial effect on vaginitis, we do not expect any health problems, side effects, or discomfort as a result of MGH.
No additional risks are foreseen for participation in the study.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)

## Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Women 18-40 years
- Primary CIN II confirmed histologically in the biopsy on colposcopic examination
- Sufficiënt mastery of the Dutch language

## Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Simultaneous abnormality in columnar epithelial cells (AIS).

- Hr-HPV negative cytology
- Immunosuppressant use/Autoimmune disease (HIV, CVID)
- History of cervical carcinoma or previous treatment for CIN (LLETZ or imiquimod)
- Pregnancy or the intention to become pregnant during the study period (6 months)
- Legal incompetence
- Known allergies to honey

# Study design

## Design

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| Study type: | Interventional |
| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |

**Primary purpose:** Treatment

## Recruitment

NL

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| Recruitment status: | Recruiting |
| Start date (anticipated): | 30-12-2024 |
| Enrollment: | 60 |
| Type: | Actual |

## Medical products/devices used

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| Generic name: | L-mesitran |
| Registration: | Yes - CE intended use |

# Ethics review

Approved WMO

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| Date: | 22-04-2024 |
| Application type: | First submission |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
| --- | --- |
| ClinicalTrials.gov | NCT06219018 |
| CCMO | NL86044.096.24 |