Simplified monitoring post-treatment.

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON27229

Source
NTR

Brief title
N/A

Health condition

Post-treatment
Cervical Intraepithelial Neoplasia (CIN)
Human papillomavirus (HPV)
methylation markers
in Dutch:
Cervicale Intraepitheliale Neoplasie (CIN)
Humaan papillomavirus (HPV)
methyleringsmarkers
follow-up

Sponsors and support

Primary sponsor: HumaVac (VU medical Center)
Source(s) of monetary or material Support: Dutch Cancer Society (KWF 2009-4413)

Intervention

Outcome measures

Primary outcome

The main study parameter is the histological confirmed recurrence of a high-grade lesion in the study population from the moment of treatment until exit-colposcopy.

Secondary outcome

Secondary study parameters include:

1. In physician obtained samples:

A. Presence of, and if applicable type of hrHPV;

B. Presence of DNA promoter methylation markers, as a precursor marker for high grade CIN lesions;

C. Results of mRNA E6E7 transcripts;

D. Result of cervical cytology.

2. In self obtained samples (self-sampling):

A. Presence of, and if applicable type of hrHPV;

B. Presence of DNA promoter methylation markers as a precursor marker for high grade CIN lesions;

C. Results of mRNA E6E7 transcripts.

3. In biopsies:

A. Presence of, and if applicable type of hrHPV;

B. Presence of DNA promoter methylation markers as a precursor marker for high grade CIN lesions;

C. Result of additional P16/Ki-67 Immunostaining for detection of high grade CIN lesions.

4. Results of behavioural questionnaire (including sexual behaviour, smoking and previous HPV- vaccination);

5. Results of questionnaire about use of self-sampling device;

6. Histological results of all endocervical samples, biopsies, LLETZ-treatment and cold-knife conisation taken.

Study description

Background summary

Background of the study:

Despite population based cervical screening still approximately 600 women are diagnosed with cervical cancer in The Netherlands each year. Another 6000 women are treated annually for the cervical cancer precursor lesions, named high-grade Cervical Intraepithelial Neoplasia (CIN2/3). Generally 10-15% of these women develop residual/recurrent cervical disease after treatment. According to the Dutch guidelines, women are monitored for residual/recurrent cervical disease by cervical cytology at 6, 12 and 24 months after treatment. However, cytology is suboptimal given its low sensitivity and specificity for residual/recurrent CIN2/3. Furthermore the many follow-up visits result in loss of adherence of women to the monitoring schedule. Besides, the low positive predictive value of cytology for post-treatment CIN2/3 leads to unnecessary diagnostic procedures (repeat smears and colposcopic examinations).

Infection with high-risk human papillomavirus (hrHPV) is necessary for the development of cervical cancer, and adding testing for high-risk human papillomavirus (hrHPV) DNA six months after treatment dramatically increased the sensitivity for post-treatment CIN2/3, while the negative predictive value of a hrHPV-negative, cytological normal smear was 99%. However, the positive predictive value of a hrHPV test was still limited, indicating that the specificity of molecular testing needs further improvement. Methylation markers, i.e. markers reflecting promoter methylation of host cell genes such as CADM1 and MAL may enhance the specificity for CIN2/3. We recently found that silencing of both tumour suppressor genes CADM1 and MAL, primarily resulting from promoter methylation, is functionally involved in cervical cancer development. Analysis of cervical biopsies showed significantly more CADM1 and MAL promoter methylation in ≥CIN3 compared with ¡ÜCIN1 lesions ($p<0.001$). Moreover, CADM1 and MAL promoter methylation was significantly more frequent in hrHPV-positive scrapings of women who developed ≥CIN2 compared to those that did not and displayed sensitivity for these lesions greater than cytology. Hence, it can be hypothesized that addition of CADM1 and MAL promoter methylation analysis during post-treatment monitoring will markedly increase the specificity for ≥CIN2. Moreover, recent studies have demonstrated that molecular testing on self-sampled cervical cells offers a reliable alternative to analysis of conventional cervical scrapings in screening programs.

Study design:
The study is designed as a multicenter prospective clinical cohort study.

Study population:

The study population (n=360) consists of women aged 18 years and above who are scheduled for a treatment for a high-grade pre-malignant cervical lesion (Cervical Intraepithelial Neoplasia (CIN) 2 or 3) by cone biopsy or colposcopic-guided LLETZ. These subjects will be recruited from women who are scheduled for cervical treatment at the Obstetrics and Gynaecology outpatient clinic of one of the participating hospitals:

1. VU University Medical Center in Amsterdam;

2. Erasmus University Medical Center in Rotterdam;

3. University Medical Center Utrecht in Utrecht;

4. Reinier de Graaf Hospital in Delft / Voorburg;

5. Sint Antonius Ziekenhuis in Nieuwegein;

6. Flevoziekenhuis in Almere;

7. Sint Lucas Andreas Ziekenhuis.

Primary study parameters/outcome of the study:

The main study parameter is the histological confirmed recurrence of a high-grade lesion in the study population from the moment of treatment until exit-colposcopy.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness (if applicable):

Risks and burden are linked to protocol procedures, such as cervical sampling and colposcopy. Although these are routine procedures, carried out by medical qualified personnel, they may cause side effects or discomfort to the subject. However, it is expected that these procedures will generally be well tolerated. The only extra burden involves the self-sampling of cervical-vaginal cells using a user-friendly self-sampling device. Self-sampling poses no threats to the physical well-being of a woman.

Study objective

Our primary objective is to determine whether testing for molecular markers, i.e. hrHPV, CADM1/MAL methylation and combinations thereof, yields a higher sensitivity and specificity for the detection of CIN2/3 or cancer after treatment in comparison with cytology.

Study design

Measurements take place at moment of cervical treatment (LLETZ or cone biopsy), and at scheduled visits at 6 and 12 months after treatment (cervical sampling by self-sampling and physician sampling).

Intervention

At time of treatment a cervical scrape will be taken for cytology testing of hrHPV and CADM1/MAL promoter methylation will be done. Six and twelve months post-treatment cervical cells will be collected by both a self-sampler and the gynaecologist and tested for

hrHPV and methylation markers. The latter scrapes will also be analysed by cytology. In case of an abnormal smear (≥BMD) and/or a hrHPV and methylation marker positive test in the physician obtained sample colposcopy will be performed and biopsies will be taken. At the end of the study, i.e. at thirteen months, a colposcopy with mandatory biopsy taking will be performed on test negative women as well. Women with residual/recurrent ¡ÝCIN2/3 disease will be treated.

Contacts

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Eligibility criteria

Inclusion criteria

1. A histological confirmed CIN2/3 lesion that will be treated by cone biopsy or colposcopic guided LLETZ;

2. Written informed consent prior to enrolment;

3. Sufficient knowledge of the Dutch language;

4. A minimum age of 18 years;

5. The intention to comply with the requirements of the protocol.

Exclusion criteria

1. The subject is pregnant (or has been in the last three months);

2. The subject has received prophylactic (or therapeutic) HPV- vaccination;

3. The subject has a diagnosis of carcinoma in cone biopsy or colposcopic guided LLETZ.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	11-01-2009
Enrollment:	360
Type:	Anticipated

Ethics review

Positive opinion

Date:	25-08-2009
Application type:	First submission

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
NTR-new	NL1852
NTR-old	NTR1964
Other	KWF : 2009-4413
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
N/A