Simplified monitoring of post-treatment CIN2/3 women by molecular testing for hrHPV and methylation markers

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cervix disorders (excl infections and inflammations)
Study type	Observational invasive

Summary

ID

NL-OMON39503

Source
ToetsingOnline

Brief title
Simplified monitoring post-treatment

Condition

- Cervix disorders (excl infections and inflammations)

Synonym
CIN, premalignant cervical disease

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: KWF (KWF 2009-4413)

Intervention

Keyword: Cervical Intraepithelial Neoplasia, Human papillomavirus, methylation markers, Post-treatment

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:

- In physician obtained samples:

• Presence of, and if applicable type of hrHPV

• Result of methylationmarker testing , i.a. CADM1/MAL

• Result of cervical cytology

- In self obtained samples (self-sampling):

• Presence of, and if applicable type of hrHPV

• Result of methylationmarker testing , i.a. CADM1/MAL

- In biopsies:

• Presence of, and if applicable type of hrHPV

- Result of methylationmarker testing , i.a. CADM1/MAL

- Results of behavioural questionnaire (including sexual behaviour, smoking and

previous HPV- vaccination)

- Results of questionnaire about use of self-sampling device

- Histological results of all endocervical samples, biopsies, LLETZ-treatment

and cold-knife conisation taken.

- Result of additional immuno-staining

The collection of aforementioned parameters aims to assess whether testing for methylation markers in conjunction with hrHPV testing is more effective in terms of sensitivity and specificity than cytology or a combination of hrHPV testing and cytology in detecting residual/recurrent CIN disease. In addition, we will investigate whether self-sampling provides a robust and more patient friendly approach for the detection of hrHPV and methylationtsting during post-treatment monitoring.

Study description

Background summary

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 <=CIN1 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 i.a. 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 objective

Our primary objective is to determine whether testing for molecular markers, i.e. hrHPV, methylationmarkers , i.a. CADM1/MAL 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

The study is designed as a multicenter prospective clinical cohort study. At treatment a cervical scrape will be taken for cytology and testing of hrHPV and methylationmarkers , i.a. CADM1/MAL . Six, twelve and twenty-four months post-treatment cervical cells will be collected by both a self-sampler and by 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, at six months post-treatment, colposcopy will be performed and biopsies will be taken. At thirteen months, a colposcopy with mandatory biopsy taking will be performed on test negative women as well. Women with residual/recurrent >=CIN2/3 disease will be treated. Twenty-four months post-treatment cervical cells will be collected by both a self-sampler and the cervical smear and tested for cytology and hrHPV and methylation markers. In case of an abnormal smear (>=BMD) and/or a hrHPV positive test a colposcopy will be performed. In case of normal cytology and a hrHPV positive test, cytology and the hrHPV have to be repeated at 36 months after treatment.In case of a neg smear and a neg HPV test the women will be sent to population based screening

Study burden and risks

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.

Contacts

Public
Vrije Universiteit Medisch Centrum

de Boelelaan 1117
Amsterdam 1081 HV
NL
Scientific
Vrije Universiteit Medisch Centrum

de Boelelaan 1117
Amsterdam 1081 HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

-A histological confirmed CIN2/3 lesion that will be treated by cone biopsy or colposcopic guided LLETZ.
- Written informed consent prior to enrolment.
- Sufficient knowledge of the Dutch language.
- A minimum age of 18 years.

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

Exclusion criteria

-The subject is pregnant (or has been in the last three months)
-The subject has received prophylactic (or therapeutic) HPV- vaccination.
-The subject has a diagnosis of carcinoma in cone biopsy or colposcopic guided LLETZ

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-01-2010
Enrollment:	360
Type:	Actual

Ethics review

Approved WMO Date:	17-12-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-09-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	15-02-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-02-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
CCMO	NL29589.029.09