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EPI-SURE: Comparing molecular and imaging techniques for the detection of womb cancer in women with abnormal bleeding

Submission date
28/05/2022

Recruitment status
No longer recruiting

Registration date
31/05/2022

Overall study status
Completed

Last Edited
07/11/2023

Condition category
Cancer

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
This trial aims to improve the diagnosis of womb (endometrial) cancer. It is the fourth most common cancer in the UK and its incidence has increased by almost 60% over the last 30 years.

There is currently no screening programme for womb cancer, and clinical assessment is led by the symptom of abnormal vaginal bleeding, which is considered a red flag. Identifying women with womb cancer with current approaches is difficult. Transvaginal ultrasound, the gold standard clinical approach, results in many women undergoing invasive confirmatory diagnostics in order to detect each case of womb cancer.

The novel WID™-qEC test, which is a molecular test based on cervical smear specimens, has been shown to be highly sensitive and specific. The performance of the WID™-qEC will be directly compared with ultrasound triage and the positive predictive value (the probability that a woman with a positive test result has womb cancer) and negative predictive value (the probability that a woman with a negative test does not have womb cancer) of the two approaches will be compared.

Who can participate?
Women aged 45 years or above who present to the Gynaecology Diagnostic Unit (Clinic 3) with abnormal bleeding or other symptoms warranting further investigation.

What does the study involve?
Each participant will require a cervical brush sample from the cervix as part of the speculum examination they undergo in their clinical assessment. They will be informed that this sample is for research only and is not part of the national cervical screening programme. Samples will be labelled with the barcode sticker and can be stored at room temperature prior to collection by UCL lab staff.

What are the possible benefits and risks of participating?
This study is altruistic, there is no remuneration to take part. Risks include a small amount of

bleeding and discomfort from the cervical brush sample. Participants will not personally benefit from taking part in the study.

Where is the study run from?
EGA Institute for Women's Health, University College London, and European Translational Oncology Prevention and Screening (EUTOPS) Institute, Universität Innsbruck, Innsbruck, Austria, Hall in Tirol, Austria.

When is the study starting and how long is it expected to run for?
January 2015 to December 2023

Who is funding the study?
The study is supported by The Eve Appeal charity (UK) and the EUTOPS Institute, University Innsbruck (Austria).

Who is the main contact?
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Additional identifiers

Integrated Research Application System (IRAS)
53431

Protocol serial number
1

Study information

Scientific Title
EPI-SURE: A comparative study of epigenetic analysis and ultrasonography for endometrial cancer detection in women presenting with abnormal vaginal bleeding

Acronym
EPI-SURE

Study objectives
The rationale for the current study is to improve the diagnosis of endometrial cancer.

Endometrial cancer is the fourth most common cancer in the UK and the number of individuals diagnosed is continuing to rise. There is no established womb cancer screening programme in the UK and clinical assessment is symptom-led. Abnormal vaginal bleeding (AVB) is considered a red flag symptom of womb cancer (particularly during the post-menopause period when this is referred to as post-menopausal bleeding). However, whilst 90% of women with womb cancer experience post-menopausal bleeding, only ~10% of women with post-menopausal bleeding have womb cancer. The current approach to identifying women with womb cancer among those presenting with post-menopausal bleeding is to initially perform a transvaginal ultrasonography, which is used to measure the thickness of the womb lining. Whilst endometrial thickness measurement can detect a high number of women with womb cancer correctly, it is less effective at correctly identifying women without the disease, and so many women with benign disease undergo further invasive diagnostic testing.

A test with a higher specificity than first-line transvaginal ultrasonography would more accurately identify and triage women with and without womb cancer. Indeed, the application of a test even earlier in the care pathway, ideally as an initial assessment via a GP, would mean that women at higher risk of womb cancer will be referred more accurately, whilst women at lower risk with benign conditions will be referred less frequently, and in turn, fewer will have to undergo invasive diagnostics in secondary care settings.

We have developed a novel test for womb cancer that, when performed on cells collected in a cervical smear, is able to detect womb cancer with both high sensitivity (i.e. the test correctly identifies the majority of patients with womb cancer) and specificity (i.e. the test correctly identifies the majority of people without the disease). The test - referred to as the WID™-qEC test - measures a specific signal which is called DNA methylation at two key genes.

The primary objective of EPI-SURE is to test the 'real world' performance (sensitivity, specificity, positive and negative predictive values) of the WID™-qEC test in comparison with transvaginal ultrasound (TVUS) as a first line triage for a cohort of women ≥45 years who present to a tertiary referral centre due to abnormal vaginal bleeding.

The secondary objectives of EPI-SURE are as follows:
1. To assess the number of procedures required in WID™-qEC true-positive and false-negative patients to reach a histological diagnosis
2. Stage, histology and grade of disease at diagnosis and relation to WID™-qEC and TVUS findings
3. Rates of inconclusive results
4. Performance of the WID™-qCIN test – a test for detecting cervical cancer

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 27/10/2014, NRES Committee London - Surrey Borders (Skipton House, 80 London Road, London, SE1 6LH, United Kingdon; +44 (0)207 104 8104; nrescommittee.london-surreyborders@nhs.net). Ref: 14/LO/1633.

Study design
Single-centre prospective cohort study

Primary study design
Observational

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Endometrial cancer

Interventions
The study intervention is a regular ThinPrep® cell sample of the cervix using a Cervex-Brush® (Rovers Medical Devices) taken by the clinician prior to the ultrasound scan. A standard Cusco speculum will be used for access and to visualise the cervix. If a woman cannot tolerate the speculum, or prefers the clinician not to use a speculum, the clinician can obtain the sample using a smaller applicator-style vaginal brush (Evalyn® - Rovers Medical Devices), that does not require a speculum.

The cervical smear collection will be carried out prior to any vaginal manipulation. Water-soluble gel lubricant may be used to reduce any discomfort. As per standard practice, gel should not be applied to the tip of the speculum. Once obtained, the brush sample will be stored in the standard PreservCyt solution labelled with a unique Participant ID code.

Explanation for the choice of comparators
Our study will compare the WID™-qEC test with ultrasonography, the current gold standard in the care of women with suspected endometrial cancer (EC). To formally classify these two methodologies, we will use the QUADAS-C risk of bias tool, which evaluates two or more index tests and compare their accuracy in relation to a reference test.

Index Test 1 is the WID™-qEC test, for which a smear sample is required (collected by a gynaecologist or a self-sample in case a woman prefers this method of sample collection). Briefly, the test measures the percentage of methylated molecules per sample at several CpG sites across 2 genes (i.e., three regions). The ThinPrep® smear sample needs to be taken before the transvaginal ultrasound (TVUS) examination.

Index Test 2 is the TVUS examination performed after the smear in consenting patients. Endometrial thickness (ET) will be measured and texture/focal lesions documented by two senior clinicians.

Reference standard in our study is histology (endometrial cancer/no endometrial cancer). The reference standard is independent of the WID™-qEC and TVUS. If anomalies are found on TVUS, transabdominal ultrasound (TAUS), Rectal US, or Saline Infusion Sonohysterography (SIS), then a small piece of tissue will be sampled either via Pipelle, hysteroscopy and biopsy, or at the time of a hysterectomy. The tissue will be examined by the histopathologists who will assign a tissue diagnosis of EC or no EC.

Intervention Type
Other

Primary outcome(s)
The 'real world' performance (sensitivity, specificity, positive and negative predictive values) of the WID™-qEC test in comparison with transvaginal ultrasound (TVUS) as a first-line triage for a cohort of women ≥45 years who present to a tertiary referral centre with abnormal vaginal bleeding. Receiver operating characteristic curves, areas under the curve, and corresponding 95% confidence intervals will be generated for both TVUS triage (according to an endometrial thickness [ET] cut off of ≥4.5 mm) and the WID™-qEC test. Sensitivity and specificity including 95% confidence intervals will be calculated, as well as the relevant positive predictive value (PPV) and negative predictive value (NPV). The ultrasound assessment as well as the Pipelle biopsy and WID™-qEC sample collection will be performed when the patient initially presents to the hospital. If hysteroscopy/endometrial biopsy and/or a hysterectomy is required, this will usually be carried out 1-4 weeks after the initial assessment.

Key secondary outcome(s))
1. To assess the number of procedures required in WID™-qEC true-positive and false-negative patients to reach a histological diagnosis, measured using ultrasound +/- Pipelle biopsy at initial presentation, and hysteroscopy/endometrial biopsy and/or hysterectomy 1-4 weeks later, respectively.
2. Stage, histology and grade of disease at diagnosis and relation to WID™-qEC and TVUS findings, measured using surgical staging of the hysterectomy specimen after a hysterectomy has been performed.
3. Rates of inconclusive results, measured using the number of diagnostic procedures carried out (ultrasound, Pipelle biopsy, hysteroscopy/endometrial biopsy, hysterectomy) throughout the patient's journey to assess the cause of abnormal vaginal bleeding.
4. Performance of the WID™-qCIN test – a test for detecting cervical cancer measured using

colposcopy and cervical biopsies at the initial presentation or once referred for colposcopy assessment.

Completion date
31/12/2023

Eligibility

Key inclusion criteria
1. Women aged 45 years or above
2. Abnormal vaginal bleeding warranting an ultrasound examination
3. Women receiving hormonal contraception, hormone replacement therapy, or other hormonal medications, such as Tamoxifen

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
Female

Total final enrolment
400

Key exclusion criteria
1. Women aged below 45 years
2. Pregnancy
3. Previous hysterectomy

Date of first enrolment
01/06/2022

Date of final enrolment
24/11/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre

University College London Hospitals NHS Foundation Trust
250 Euston Road
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Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
University/education

Funder Name
The Eve Appeal

Funder Name
Universität Innsbruck

Alternative Name(s)
University of Innsbruck, uibk

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
Austria

Results and Publications

Individual participant data (IPD) sharing plan

Current Individual participant data (IPD) sharing plan as of 31/10/2023:
Anonymised individual-level patient data can be provided to researchers upon written request 24 months after publication of the Article. A detailed proposal for how the data will be used should be sent to the corresponding author and is required to allow assessment of the application.

Previous Individual participant data (IPD) sharing plan:
The datasets generated and/or analysed during the current study will be published as a supplement to the subsequent results publication. Participants will be asked to offer their consent for anonymised data to be shared.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		06/11/2023	07/11/2023	Yes	No
HRA research summary			28/06/2023	No	No
Other publications		06/11/2023	07/11/2023	Yes	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes