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Comparing gonadotrophin-releasing hormone analogues with repeat laparoscopic surgery for the treatment of recurrent pain following surgery for endometriosis

Submission date
17/11/2021

Recruitment status
No longer recruiting

Registration date
18/11/2021

Overall study status
Completed

Last Edited
10/01/2022

Condition category
Urological and Genital Diseases

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Endometriosis is a common condition that affects one in ten women from puberty to menopause. It occurs when cells similar to those lining the womb grow outside it, generally within the pelvis. These cells behave like the cells lining the womb, causing internal bleeding at the time of periods, scarring and pain. It is diagnosed by laparoscopy (keyhole surgery) which identifies areas of endometriosis that can then be surgically destroyed or removed. However, surgery rarely provides lasting relief and pain can return in up to half of treated women within 5 years. To reduce the chance of regrowth of endometriosis and recurrence of pain, women who are not trying to get pregnant are offered the combined oral contraceptive pill or other contraceptives containing hormones called progestogens. Despite this, about one in three women will require more operations to treat endometriosis that has come back.
Endometriosis depends on the female hormone oestrogen (produced by the ovaries) for growth. Removing the ovaries (often along with the womb) therefore provides the best chance of pain relief and least chance of more operations but is not an option for many premenopausal with endometriosis. A less invasive way of shrinking endometriosis is to use a drug called gonadotrophin-releasing hormone analogue (GnRHa) which temporarily stops the ovaries from producing oestrogen. While very effective in terms of reducing pain, this treatment has only been used for up to a year because of side effects such as hot flushes and night sweats and concerns about osteoporosis (thinning of the bones). Recent research has shown that adding small doses of hormone replacement therapy (HRT) in women on GnRHa reduces the risk of side effects and osteoporosis whilst controlling the pain. The aim of this study is to compare long-term GnRHa with added HRT to further keyhole surgery for the treatment of endometriosis in women who experience recurrence of pain after surgery but wish to preserve their fertility.

Who can participate?
Women aged between 21-49 years old who have recurrent pain following laparoscopic treatment for endometriosis and who wish to avoid removal of their ovaries and a hysterectomy

What does the study involve?
Women who decide to take part will be randomly assigned (using a computer) to join one of the two study groups, either keyhole surgery to remove or destroy endometriosis or GnRHa with add-back HRT for 2 years. When they join the study they will be asked to complete a questionnaire about their pain and quality of life. Every 6 months for 2 years, they will be asked to complete additional questionnaires about their pain, quality of life and any treatment they have had for endometriosis (four additional questionnaires in total). Women in the GnRHa with add-back HRT group will have three DEXA scans (at recruitment and 12 and 24 months after recruitment) to evaluate the impact of the GnRHa treatment on the strength of their bones. Some women in the surgical group will have two DEXA scans, one at recruitment and one 24 months after.

What are the possible benefits and risks of participating?
Women will receive the same health care from their doctor whether or not they choose to participate in the study. By taking part, they will be directly helping the researchers to find the best treatment for women with recurrence of pain following surgery for endometriosis and helping women who have this condition in the future. The results of the study will also help plan effective services offered to women with endometriosis.
The researchers do not think that there are any possible disadvantages in taking part in this study. Whichever treatment they are allocated, this will be performed by a competent and trained clinician. There are risks associated with all procedures, anaesthetics and medications. Steps are always taken to ensure that these risks are minimised. As part of routine care, they will be well informed of potential risks. They will not be able to participate in other drug studies or surgical studies at the same time.

Where is the study run from?
University of Aberdeen (UK)

When is the study starting and how long is it expected to run for?
August 2019 to January 2024

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Dr Suzanne Breeman
regal@abdn.ac.uk

Study website
https://w3.abdn.ac.uk/hsru/REGAL

Contact information

Type(s)
Scientific

Contact name
Dr Lucky Saraswat

Contact details

Ward 315, Department of Gynaecology
Aberdeen Royal Infirmary
Foresterhill Road
Aberdeen
United Kingdom
AB25 2ZN
+44 (0)1224 553471
lucky.saraswat@nhs.scot

Type(s)
Scientific

Contact name
Dr Suzanne Breeman

ORCID ID
http://orcid.org/0000-0001-9950-7079

Contact details
Centre for Healthcare Randomised Trials (CHaRT)
University of Aberdeen
Health Sciences Building
Foresterhill
Aberdeen
United Kingdom
AB25 2ZD
+44 (0)1224 438169
s.breeman@abdn.ac.uk

Additional identifiers

EudraCT/CTIS number
2020-005466-33

IRAS number
271703

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 50851, IRAS 271703

Study information

Scientific Title
Recurrence of endometriosis: a randomised controlled trial of clinical and cost-effectiveness of gonadotrophin-releasing hormone analogues with add-back hormone replacement therapy versus repeat laparoscopic surgery (REGAL)

Acronym
REGAL

Study objectives
1. Determine whether the long-term use of gonadotrophin-releasing hormone analogues (GnRHa) with add-back hormone replacement therapy (HRT) is an effective treatment to further laparoscopic surgery for excision or ablation of endometriosis in women who present with recurrence of pain following previous surgery
2. Assess the cost-effectiveness of GnRHa with add-back HRT compared to laparoscopic ablation or excision

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 05/03/2021, East of Scotland Research Ethics Service (EoSRES) (Tayside Medical Science Centre, Residency Block Level 3, George Pirie Way, Ninewells Hospital and Medical School, Dundee, DD1 9SY, UK; +44 (0)1382 383878; tay.eosres@nhs.scot), REC ref: 21/ES/0005

Study design
Randomized; Interventional; Design type: Treatment, Screening, Drug

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
The Participant information sheet will be available on the study website https://w3.abdn.ac.uk/hsru/REGAL

Health condition(s) or problem(s) studied
Endometriosis

Interventions
Women who experience recurrence of pain following previous laparoscopic treatment for endometriosis will be invited to take part. Women will be referred by their GP to specialist endometriosis centres and will be invited to take part by the endometriosis team.

Potentially eligible women will be given information about the study. Those who are interested in taking part will be asked to sign a consent form. Baseline data will be collected, and women will be asked to complete a questionnaire about their condition and their quality of life.

After consent, women will be randomised to either GnRHa (with HRT) or for further laparoscopic surgery.

For women randomised to GnRHa (with HRT), the GnRHa can be administered through various routes including intramuscular injections or subcutaneously monthly or every 12 weeks. The HRT can be given orally, transdermally or via the intrauterine system.

GnRHa and HRA will not be specifically manufactured or labelled for use within the REGAL trial. The trial will use routine stocks prescribed by the endometriosis team or their GP and dispensed by the hospital or local pharmacy.

For women randomised to GnRHa (with HRT), bone mineral density will be monitored by DEXA scans at baseline, 12 and 24 months.

Women who are randomised to laparoscopic surgery will be added to the waiting list for surgery.

The researchers will ask women to complete questionnaires every 6 months to collect information on pain, quality of life, compliance with treatment and any side effects.

There is a qualitative sub-study. The first involves audio-recording consultations - women will receive information about this in advance of the consultation and will be asked to give verbal agreement for the recording at the start of their consultation. There will also be interviews with women and study teams. Potential participants will be provided with information and if they agree to take part, verbal agreement for the interview will be sought at the beginning of the interview. The qualitative sub-study will identify challenges relating to the design and conduct of the trial, particularly around recruitment.

Intervention Type
Mixed

Primary outcome measure
Clinical:
Endometriosis-associated pain measured using the pain domain of the condition-specific Endometriosis Health Profile-30 (EHP-30) at 24 months

Economic:
Incremental cost per QALY gained from a health service perspective, measured using self-completed questionnaires and case note reviews at 24 months post-randomisation

Secondary outcome measures
Clinical:
1. Bone mineral density (BMD) measured using Dual Energy X-ray absorptiometry (DEXA) scan for a subgroup of patients (90 women in each arm across a minimum of 5 centres ideally recruited over 18 months). For the GnRHa group BMD will be measured at baseline, 12 and 24 months post-randomisation, for the laparoscopic surgery group at baseline and 24 months post-randomisation
2. Surgical and anaesthetic complications and adverse events assessed using self-completed questionnaires and case note reviews at 24 months post-randomisation

Patient-reported (measured using self-completed questionnaires at 6, 12, 18 and 24-months post-randomisation unless stated otherwise):
1. Adverse events that are a result of treatment for endometriosis

2. Endometriosis treatment received
3. Generic and condition-specific quality of life, measured using EQ-5D and EHP-30 at baseline, 6, 12, 18 and 24 months post-randomisation
4. Endometriosis-associated pain measured using the pain domain of EHP-30 at 6, 12, and 18 months
5. Patient satisfaction measured on a six-point scale from 'totally satisfied' to 'totally dissatisfied'
6. Further pharmacological treatment (change of hormonal treatment, increased use of analgesics, start of neuromodulators such as pregabalin, gabapentin, amitryptiline) or surgery for endometriosis or other treatments (e.g. acupuncture, CBT) for endometriosis-associated pain
7. Pregnancy

Overall study start date
01/08/2019

Completion date
31/01/2024

Eligibility

Key inclusion criteria
1. Women aged 21–49 years with recurrent pain following laparoscopic surgery for endometriosis (excision or ablation) who wish to avoid removal of ovaries and hysterectomy, irrespective of site and stage of endometriosis, number of previous surgeries or use of post-operative hormonal treatment.
2. Women who are considered suitable for both treatment arms
3. Able and willing to give informed consent to participate and to participate in study procedures, including DEXA scans
(There are provisions within the protocol for recording consent from patients who are not able to read or write (but who have the capacity and who can speak English sufficiently to understand the information being provided orally)
4. Willing to undergo a pregnancy test prior to intervention

Participant type(s)
Patient

Age group
Adult

Sex
Female

Target number of participants
Planned Sample Size: 400; UK Sample Size: 400

Key exclusion criteria
1. Previous diagnostic laparoscopy only (no treatment to endometriosis)
2. Planning to conceive in the next 2 years
3. Current pregnancy or breastfeeding
4. Previous bilateral oophorectomy
5. Current or recent (within the last 3 months) users of GnRHa

6. Contraindicated concomitant medications with GnRHa. These are women currently using hormonal contraceptives who are unwilling to stop their use during the follow-up period (for example, progesterone only pill, combined oral contraceptive pill, depo injection or contraceptive implant); medicinal products that raise prolactin levels (for example domperidone, metoclopramide, haloperidol, risperidone and sulpride); and medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (for example quinidine, disopyramide) or class III (for example amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics).
7. Hypersensitivity to GnRH (gonadotropin-releasing hormone), its analogues or to any of the excipients
8. Women at high risk of serious adverse effects with GnRHa such as a confirmed diagnosis of osteoporosis
9. Women with risk factors for osteoporosis such as chronic alcohol abuse, current heavy smokers over 20 cigarettes per day, long-term therapy with drugs that reduce bone mineral density currently or in the last 3 months, such as anticonvulsants or oral corticosteroids (2.5mg per day), family history of osteoporosis, and malnutrition, e.g. anorexia nervosa
10. Diagnosis of severe depression in the last 10 years. For the purposes of REGAL, severe depression includes but is not limited to suicidal thoughts, requirement for hospitalisation and symptoms that make it almost impossible to get through daily life
11. Contraindications for add-back HRT use: these are women with a personal history of breast cancer, known carriers of BRCA 1 and 2, personal history of venous thromboembolism or women with known inherited thrombophilia (e.g.: Factor V Leiden, Protein C or S or Antithrombin deficiency, Prothrombin gene mutation)

Date of first enrolment
01/09/2021

Date of final enrolment
28/02/2023

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
NHS Grampian
Summerfield House
2 Eday Road
Aberdeen
United Kingdom
AB15 6RE

Study participating centre
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Sponsor information

Organisation
NHS Grampian

Sponsor details
Grampian Health Board
Research & Development Office
Foresterhill House Annexe
Foresterhill
Aberdeen
Scotland
United Kingdom
AB25 2ZB
+44 (0)1224 551121
gram.randd@nhs.scot

Sponsor type
Hospital/treatment centre

Website
http://www.nhsgrampian.org/

ROR
https://ror.org/00ma0mg56

Organisation
University of Aberdeen

Sponsor details
Research Governance Office
Room 1.126
Polwarth Building
Foresterhill
Aberdeen
Scotland
United Kingdom

AB25 2ZD
+44 (0)1224437220
researchgovernance@abdn.ac.uk

Sponsor type
University/education

Website
http://www.abdn.ac.uk/

Funder(s)

Funder type
Government

Funder Name
NIHR Central Commissioning Facility (CCF)

Results and Publications

Publication and dissemination plan
1. The protocol can be viewed on the study website https://w3.abdn.ac.uk/hsru/REGAL
2. Planned publication in a high-impact peer-reviewed journal

Intention to publish date
01/01/2025

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No