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What are the effects of a 16-week exercise program on ovarian function in women with morbid obesity who have undergone bariatric surgery?

Submission date
30/09/2019

Recruitment status
No longer recruiting

Registration date
04/10/2019

Overall study status
Completed

Last Edited
21/06/2022

Condition category
Nutritional, Metabolic, Endocrine

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

Plain English summary of protocol

Background and study aims
Over 300,000 women in Spain have morbid obesity, which means that obesity is affecting or is likely to affect their daily life and health. Morbid obesity is associated with problems with ovulation (when the ovary releases an egg during a woman's monthly cycle), which can affect fertility and lead to problems such as excess weight gain and hair growth that can affect quality of life. Bariatric surgery (surgery to increase weight loss by reducing the amount of food that can be eaten or absorbed, such as gastric band or gastric sleeve surgery) might improve ovulation, but adding physical exercise in the follow-up period after surgery might further improve ovarian function. This study will investigate the effects of a carefully prescribed exercise intervention combining resistance and aerobic training, starting approximately 7 days after bariatric surgery, on ovarian function in 40 women with morbid obesity. The effects on physical processes that alter ovulation in the presence of obesity (such as insulin resistance, inflammation, or arterial stiffness), as well as physical fitness, body composition and quality of life will also be assessed.

Who can participate?
Women aged 18 to 45 with morbid obesity, or severe obesity with associated illnesses, who are expecting to undergo bariatric surgery.

What does the study involve?
Participants will be randomly allocated to a usual-care group or an exercise group. Both groups will follow international guidelines for the follow-up of bariatric surgery,. The exercise group will also have one-to-one personal training for 16 weeks (3 sessions of 60 minutes each week) combining resistance and aerobic training, and following the instructions regarding duration, frequency, volume, intensity, progression, and adaptability to the patient recommended by international institutions. The participants will be assessed before surgery, after the 16-week intervention, and at 1 year after surgery. These assessments will involve blood tests, transvaginal ultrasound, questionnaire, fitness measurements and personal interviews.

What are the possible benefits and risks of participating?
Possible benefits include improving ovulation function, as well as improved fitness, body composition (proportions of fat and muscle in the body) and quality of life. Potential risks are those associated with exercise, such as potential injuries. However, this is very unlikely to occur as all sessions will be closely supervised by qualified trainers.

Where is the study run from?
University of Almería (Spain)

When is the study starting and how long is it expected to run for?
January 2019 to September 2022

Who is funding the study?
Spain's Ministry of Science, Innovation and Universities

Who is the main contact?
1. Dr Alberto Soriano-Maldonado, asoriano@ual.es
2. Dr. Ana María Fernández Alonso, anafernandez.alonso@gmail.com

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
RTI2018-093302-A-I00

Study information

Scientific Title
Physical Exercise following bariatric surgery in women with Morbid obesity: effects on OVARian function and mechanistic insights (EMOVAR)

Acronym
EMOVAR

Study objectives
The main hypothesis of this study is that a supervised exercise program, focused primarily on muscular and aerobic training, will improve ovarian function and several mechanisms involved in ovulation such as inflammation, insulin resistance and arterial distensibility in women with severe /morbid obesity undergoing bariatric surgery. Other secondary outcomes, such as physical fitness, body weight and composition, and health-related quality of life will likely improve as a result of the intervention.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 30/01/2019, Almería Research Ethics Committee (Calle Hermandad de Donantes de Sangre, 04009, Almería, Spain; +34 950 016 000; al42_cetico_cht.hto.sspa@juntadeandalucia.es), ref: RTI2018-093302-A-I00; 7/2019

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a participant information sheet.

Health condition(s) or problem(s) studied
Severe/morbid obesity

Interventions
Randomization.
Patients will be randomly assigned to the groups. A simple randomization sequence will be generated by computer, which will represent the allocation of each participant, and will be introduced in sealed, opaque envelopes, numbered in sequential order that will correspond to the order in which participants will be randomized. Each participant will be randomized (the corresponding envelope will be opened in front of the participant) at medical discharge, that is, after having fulfilled the inclusion criteria, signed informed consent, performed baseline evaluation and after having undergone bariatric surgery. The intervention will start approximately 7 days after medical discharge.

Exercise Group.
The patients assigned to the Exercise Group (EG) will carry out a supervised exercise program of 48 sessions distributed in 16 weeks with a frequency of 3 sessions per week and a volume of 1 hour per session. The exercise program will combine resistance and aerobic training in the same session (i.e. concurrent training). The exercise program will comply with international recommendations for resistance and aerobic training, following criteria for effective and safe progression. In order to standardize the protocol and maximize its transparency and replicability, the guidelines stated in the Consensus on Exercise Reporting Template (CERT), which describes all the parameters that should be reported in a physical exercise program, will be followed. The training sessions will be individual and will be held in the sports facilities of the University of Almería. All sessions will be supervised by a Personal Trainer with a degree in Physical Activity and Sports Sciences, with Master training in Personal Training or at least 2 years of experience carrying out exercise programs with obese people.
The training sessions will consist of an initial warm-up of 10 min, a main part of 45 min (core compensatory exercises, range of movement and stabilizing muscles, followed by concurrent training), and a 5-minute cool down with dynamic and static flexibility exercises. The warm-up will combine 5 min of aerobic exercise on a treadmill and 5 min of basic movement patterns and / or core and stabilization exercises. The main part will be a combination of a strength training block and an aerobic training block. The exercises will progress in complexity and intensity in a personalized way throughout 4 phases: familiarization phase (week 1 to 4), phase 1 (weeks 5-8), phase 2 (weeks 9-10), phase 3 (weeks 11-16). Regarding strength training, participants will learn basic movement patterns and perform strength exercises with body weight and elastic bands in the familiarization phase. Exercises aimed at adapting to the resistance exercises that will be

performed with external weight in the following phases will also take place in the familiarization phase. From phase 1, exercises with external loads will be carried out and the intensity of the load will progress from 50% to 75% of a Maximum Repetition (RM), quantified by the character of the effort (CE; i.e. based on the maximum number of repetitions that the patient actually performs out of the maximum number of repetitions that could be performed with a given load). There will be a total of 6 strength exercises focused on large muscle groups and main movement patterns: squats, lat pull-down to the chest, bench press, low pulley row, deadlift, and push press. Participants will complete one set for each exercise during the first weeks of phase 1 of the program and will progress to two and three sets in phases 2 and 3, respectively. Maximum possible movement velocity will be required in each repetition. Resting periods between sets will be 30-60 s. With respect to aerobic training, continuous aerobic training will be carried out in the familiarization phase with a volume of 10 to 15 min (between 50-65% of the heart rate reserve; HRR) in phase 1, progressing up to 25 min at 75% of the HRR in phase 3. Exercise intensity of the aerobic training will be controlled by heart rate monitor (Polar V800) and by rating of perceived exertion (RPE; Borg CR-10 scale), and the OMNI-Resistance training Scale will be used for controlling strength training intensity.
Adherence to the exercise program will be assessed throughout the intervention period with a registration sheet designed ad hoc and will be completed daily by the personal trainer in each session. In addition to the percentage of attendance ([No. of attended sessions/No. of planned sessions] × 100), other variables such as punctuality, physical activity outside the program, the number and type of adverse events, or the compliant attitude during the session will be recorded. The RPE, mood and sensation of acute exhaustion induced by exercise will be recorded to try to anticipate (where appropriate) possible symptoms of fatigue or dissatisfaction and make appropriate adjustments. Strategies to maximize adherence will include sending motivational messages (once per week) and videos (once per month) through WhatsApp.

Control or usual care group.
Participants assigned to the usual care group will receive international guidelines for a healthy lifestyle following bariatric surgery, established by the American Association of Clinical Endocrinology, the Obesity Society and the American Society for Bariatric and Metabolic Surgery.

Intervention Type
Behavioural

Primary outcome measure
Plasma level of sex hormone binding globulin (SHBG) at baseline and 16-week and 1-year follow-up measured by immunoassay with a Beckman Coulter kit, with a maximum value of 200 nmol/l and an imprecision of less than 7%

Secondary outcome measures
All outcomes will be assessed at baseline, as well as at follow-up (i.e. week 16 and 1 year)

Secondary outcomes related to ovarian function (primary aim):
1. Plasma level of anti-Müllerian hormone (AMH) measured using an ELISA assay (antimüllerian hormone Gen II ELISA assay; Beckman Coulter, Brea, CA, USA), with a detection limit of 17 pmol /l, and with a coefficient of variation of less than 10%
2. Plasma level of follicle-stimulating hormone (FSH), as a marker of ovulatory capacity, measured using the Beckman Coulter immunoassay kit, with a sensitivity of 0.2 mIU/ml, with an imprecision of less than 10%
3. Plasma level of thyroxine (T4; ng/dl) measured in the laboratory using a Beckman Coulter

immunoassay kit
4. Plasma level of thyrotropin (TSH; µIU/l), as a marker of thyroid function, measured in the laboratory using a Beckman Coulter immunoassay kit, with a detection limit of 100 mUI/l and a coefficient of variation of 0.003 µUI/ml
5. Plasma level of luteinizing hormone (LH; mUI / l) measured using a Beckman Coulter immunoassay kit, with a detection limit of 250 IU/l with a coefficient of variation of 0.2 mIU/ml
6. Plasma level of estradiol (pmol/l) measured in the laboratory using Beckman Coulter immunoassay kit
7. Plasma level of prolactin (ng/ml) measured using a Beckman Coulter immunoassay kit
8. Plasma level of total testosterone (ng/ml) measured using a Beckman Coulter immunoassay kit, with a detection limit of 16 ng/ml with a coefficient of variation of 0.1 ng/ml
9. Free androgenic index will be calculated as the total testosterone:SHBG ratio

Outcomes obtained by transvaginal ultrasound using the Toshiba Xario ultrasound equipment (Toshiba Medical Systems Corporation, Japan) equipped with a 7 MHz curved endovaginal transducer.
10. Ovocitary count. The total number of follicles whose size is between 2 and 8 mm ultrasound visualized in both ovaries will be recorded.
11. Diameters of both ovaries measured sonographically in the longitudinal axis and in the transverse axis (mm)
12. Endometrial thickness: measurement of the thickness of the endometrium ultrasound visualized in a longitudinal section of the uterus.
13. Pulsatility index of uterine arteries (left, right and middle), measured by ultrasound. The 7 MHz endovaginal transducer must be placed paramedially to the uterine cervix at the level of the internal cervical orifice. The vessel must be identified with color Doppler and high speed scales (between 30 and 50 cm/s) should be used for the selective identification of the vessel. The soundproofing angle for measurements must be less than 45°. Three or more waves of similar characteristics must be obtained for measurement, with adequate magnification, occupying at least three quarters of the screen. The size of the Doppler sample should be equivalent to the diameter of the artery and should be placed in the center of the vessel. The pulsatility index (PI) will be calculated.

Other variables relevant to to ovarian function:
14. Duration of menstrual bleeding (days) recorded by the gynecologist through personal interview with the participant
15. Duration of the menstrual cycle (days) recorded by the gynecologist through personal interview with the participant
16. Hirsutism measured using the Ferriman and Gallwey Scale. The score will be: ≤8: normal; 9-11: mild hirsutism; 12-9: moderate hirsutism; ≥20: severe hirsutism

Secondary outcomes related to secondary aims (i.e. markers of chronic inflammation and insulin resistance) obtained in plasma:
17. C-reactive Protein (CRP) levels (mg/l), as a relevant indicator of systemic inflammation, measured using an immunoturbidimetric analysis with the Beckman Coulter kit, with a detection limit of 80 mg/l with a coefficient of variation <1 mg/l
18. Interleukin 6 (IL-6; pg/ml) measured using a Cobas immunoassay kit, with a sensitivity of 1.5 pg/ml
19. Tumor necrosis factor alpha (TNFα; pg/ml) measured using a Cobas immunoassay kit, with a coefficient of variation of less than 8%
20. Leptin (pg/ml) measured using a Cobas immunoassay kit, with a coefficient of variation of less than 6%
21. Glomerular sedimentation rate (VSG, mm/h). It will be measured by Menarini diagnostics kit

22. Glucose and insulin measured using standard techniques. The HOMA index (homeostasis model assessment of insulin resistance) will be calculated using the formula [insulin, mIU/l] × [glucose, mg/dl])/405. Insulin is measured using the Cobas immunoassay kit, with an upper limit of 300 µUI/ml with a coefficient of variation of 0.03 µIU/ml.

Other secondary outcomes:
23. Arterial stiffness measured through pulse wave velocity (VOP; Mobil-O-Graph® 24-h pulse wave analysis monitor, IEM GmbH, Stolberg, Germany). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) will be measured with the same device and the mean blood pressure will be calculated as MBP =1/3(SBP - DBP) + DBP.
24. Body composition assessed by dual x-ray absorptiometry (DEXA; DMS Imaging, STRATOS dR). The percentage of total body fat, fat free mass and muscle mass will be measured.
25.Weight measured using an InBody270 body composition analyzer
26. Height measured using a Seca 22 stadiometer
27. Aerobic capacity (or cardiorespiratory fitness) assessed with the Bruce protocol on a treadmill
28. Lower limb muscular strength assessed with the 30-s chair stand test
29. Upper limb muscular strength assessed using handgrip dynamometry (i.e. handgrip strength test)
30. Range of motion of the shoulder girdle assessed using the back-scratch test
31. Health-related quality of life assessed with the 36-item Short Form Health Survey (SF-36) questionnaire. The score in its 8 dimensions and a physical and mental component summary (i.e. the score ranges from 0 to 100, with higher values representing a better quality of life) will be calculated.

Other information that will be registered:
32. Physical activity and sedentary time assessed using an ActiGraph activity monitor with ActiLife software version 6.11.7
33. Food intake assessed (at pre-test, post-test and 12-month follow-up) using two 24-h reminders
34. Frequency of food consumption assessed with the self-administered questionnaire used in the PREDIMED study
35. Adherence to the Mediterranean diet will be assessed with the PREDIMED questionnaire
36. Sociodemographic variables and clinical history: Age, marital status, level of education, employment status, income level, etc. will be recorded.
37. Personal history of obesity (duration of obesity), cardiovascular disease, hypertension, obstructive sleep apnea (OSA), type 2 diabetes, medication use, etc., assessed using the patient's medical history
38. Surgical technique assessed using patient's medical record. The surgical techniques to be performed are mini-gastric bypass with a single anastomosis (mainly), as well as laparoscopic sleeve gastrectomy (only when BMI ≥50).

Overall study start date
01/01/2019

Completion date
13/09/2022

Eligibility

Key inclusion criteria

1. Women aged 18 to 45 years
2. Body Mass Index (BMI) ≥40 kg/m2 or ≥35 kg/m2 with comorbidities
3. Acceptable surgical risk (defined by the anesthetist's approval)
4. Obesity maintained for at least 5 years
5. Failure of previous treatments
6. Informed consent signed for surgical treatment
7. No contraindications to performing supervised physical exercise, defined as answering 'no' to all the questions in the Physical Activity Readiness Questionnaire
8. Reside in Almería or (alternatively) can commit to attend training sessions 3 times per week for 16 weeks if assigned to the exercise group

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
40

Key exclusion criteria
1. Serious psychiatric disorders such as schizophrenia, personality disorders, eating disorders, untreated depression or suicidal tendencies
2. Neurological disorders that may interfere with physical exercise
3. Adrenal or thyroid pathology that may be the cause of obesity
4. Uncontrolled addiction to alcohol or drugs
5. Presence of hysterectomy and / or previous adnexectomy
6. Active inflammatory or infectious disease

Date of first enrolment
15/10/2019

Date of final enrolment
01/09/2021

Locations

Countries of recruitment
Spain

Study participating centre

Universidad de Almería
Ctra. Sacramento s/n
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Study participating centre
Torrecárdenas University Hospital
Calle Hermandad de Donantes de Sangre, s/n
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Study participating centre
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University/education

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ROR
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Funder(s)

Funder type
Government

Funder Name
Ministerio de Ciencia, Innovación y Universidades de España [ref: RTI2018-093302-A-I00]

Results and Publications

Publication and dissemination plan
The results will be presented at national and international conferences and will be published in peer-reviewed international journals without restriction.

Intention to publish date
15/06/2023

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will not be publicly available. Proposals should be directed to the principal investigator (PI) Dr Alberto Soriano-Maldonado (asoriano@ual.es). To gain access, data requestors will likely need to sign a data access agreement. The data will be shared with investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose. Individual participant data underling the results reported in the published article after deidentification (text, tables, figures and appendices) will be shared. The data will be available from 9 months to 36 months following article publication. The data will be shared to achieve specific aims in the approved proposal and co-authorship might be requested.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	01/03/2020	23/03/2020	Yes	No