1 General Information

1.1 Study identification

Title:

Physical Activity in Bed Rest Hospitalized High-Risk Pregnant Women.

Codi o número d'identificació del protocol: Bed RestPregnancy

Versió i data: v02, 31/07/2024

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2 State of the Art

Physical activity during pregnancy is safe and is associated with a variety of health benefits for mother and baby/fetus[1]: The results of systematic reviews identified that, compared with no physical activity (PA), accumulating at least 150 min of moderate-to-vigorous intensity PA over three or more days per week was associated with clinically meaningful reductions in the odds of developing gestational diabetes mellitus, pre-eclampsia, and gestational hypertension[2] and improves mental health and quality of life[34]. Despite the known health benefits of PA, yet few women engage in sufficient activity during pregnancy and so far, pregnancy is a time of marked decline in PA levels[5]. To provide women with reliable and trustworthy information, and to encourage greater participation in PA during pregnancy, many governments have developed guidelines for PA during pregnancy[6]. However, the actual fulfillment of these recommendations seems to be low[7,8].

While this is true for pregnancy overall, PA is indeed dramatically restricted when high-risk pregnancy conditions may warrant bed rest or hospitalization. Overall, guidelines indicate absolute or relative contraindications to perform mean-to-vigorous PA in pregnancy complications although individuals should continue their usual activities of daily living[1]. Despite of these recommendations, individuals who develop complications during pregnancy have traditionally been prescribed activity restriction (the most severe form being complete bed rest) which could lead to a true sedentary lifestyle. So much so that despite the lack of evidence of the benefits of the activity restriction, it has been reported that up to 87% of North American clinicians would still prescribe bed rest for high-risk pregnant individuals for lack of better therapeutic options[9]. Indeed, women do tend to be 100% compliant with these recommendations leading to one third of pregnant women being restricted in her daily activity at some point during pregnancy[5,10]. Although some efforts have been given to counteract this sedentarism, the level of the recommendations to exercise are heterogeneous in terms of quantity and intensity depending also on physicians' beliefs.

Impact of severe restriction of PA as the one due to micro-gravity in astronauts has been studied[11]. Muscle loss may appear as soon as after 5-days in bed rest[12] which makes a planned exercise program to counteract deconditioning mandatory. An extensive list of side-effects for every system have been described to occur due to the inactivity (fatigue, headache, mood changes, lower back pain, tenseness, difficulty concentrating, back muscle soreness, dry skin, cardiac atrophy, augmented heart rate, blood coagulation, heartburn and reflux, constipation, diminished lung compliance, decreased cardiac output and stroke volume, muscle atrophy, bone demineralization, joint contracture, thromboembolic disease, skin ulcers, glucose intolerance, skeletal muscle insulin resistance, and increased concentrations of blood cholesterol and triglycerides)[11]. Many of these side-effects appear in activity-restricted pregnant individuals who have been hospitalized due to a high-risk pregnancy, but this has not been fully studied[13–15] as focus has been put on perinatal outcomes[16–20] and not on physiological changes. Indeed, considering that also physical (hormonal, respiratory, cardiovascular, and skeletal) modifications and psychosocial (stress, anxiety, and depression) changes occur in normal pregnancy, pregnant individuals who are restricted in their daily activity or confined to bed rest due to complications, may potentially present even more deep alterations. Also, sleep duration and quality get worse[21] and depression, anxiety, stress, perception of loss of self-control and boredom increase[22]. Overall, the severity of these side-effects appears to be directly related to the degree of activity restriction[23] . Therefore, all these changes may jeopardize their ability to resume an inevitable demanding activity in the postpartum period.

On the other hand, there are studies that suggest exercise prescription may counteract deconditioning in non-pregnant females on bed rest. In this population, resistance exercise and

passive stretching of muscles may be a successful countermeasure to diminish cardiovascular deconditioning[24,25] and bone deterioration accumulated during bed rest[26–28]. Therefore, although there are no studies to evaluate these improvements in pregnant individuals subjected to activity restriction, we could hypothesize that a dedicated combined resistance and strength exercise program could be proposed to prevent these changes to occur. Although some efforts are being made to overcome absolute restriction of the physical activity when medical complications appear during pregnancy[29], only few data are available to design an adequate exercise routine[30] which could potentially prevent from deconditioning during activity restriction and improve emotional experience for those women that need to be at bed rest in home or hospitalized. Indeed, considering that pre-habilitation programs have been proved to be of benefit to individuals which will be undergoing oncologic or major abdominal surgery,[31–33] an exercise program could potentially also be of benefit in those pregnant women in bed rest who will need to overcome in a near future the major changes that entails delivery and postpartum.

In summary, benefits of physical activity in a normal pregnancy to prevent medical complications and mental health disorders have been proved. Therefore, benefits could be potentially higher if a specifically designed exercise program was performed by the group of pregnant women to who bed rest and/or hospitalization has been indicated. Indeed, maintaining a certain degree of fitness could potentially help to resume activity in the postpartum period when physical and emotional needs of the woman are increased.

The experts on the topic acknowledge the lack of studies evaluating the effects of bed rest and different types of physical activity/exercise intervention on medical complications during pregnancy. Data suggest the importance of some type of activity over none and urge for future research.[34,35]

More research is necessary to improve the health of those individuals who are hospitalized during pregnancy and urgent research is needed to evaluate the benefits of a specifically designed exercise program for women who have high-risk pregnancies and are severely activity restricted. Therefore, this is a knowledge-generating project aligned with the opportunity to reduce inequity and address this health issue from a gender perspective, given that the proposed topic fully impacts in women's health.

A pilot RCT is necessary as a first step in order to evaluate acceptability and feasibility of the intervention and determine effect-size to assess future sample-size calculations to support the adequate design for an RCT.[36]

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3 Hypothesis

MAIN HYPOTHESIS

The performance of a specifically designed exercise program (based on resistance/strength, designed to be executed while in bed) in a group of bed rest hospitalized pregnant individuals helps to improve its physical and emotional health and perception of health (including quality of life and sleep) during hospitalization compared to a control group in which a standard management (not including an structured exercise program) is carried out.

Hypothesis 1

Performing the specifically designed exercise program is associated with better maintenance of the **physical condition** after 1, 2 or 3 weeks of hospitalization before delivery and 6weeks postpartum, compared to a no-exercise group.

Hypothesis 2

Performing the specifically designed exercise program is associated with better maintenance of the **mental/emotional condition** after 1, 2 or 3 weeks of hospitalization before delivery and 6weeks postpartum, compared to a no-exercise group.

Hypothesis 3

Performing the specifically designed exercise program is associated with better **perception of health, including quality of life and sleep**, after 1, 2 or 3 weeks of hospitalization before delivery and 6weeks postpartum, compared to a no-exercise group.

SECONDARY HYPOTHESIS

The inclusion of a specifically designed exercise program (based on resistance/strength, designed to be executed while in bed) is well accepted, feasible and perceived as a good experience in a group of bed rest hospitalized pregnant individuals.

Hypothesis 4

The recruitment rate of a study of these characteristics is higher than 50% of the eligible women.

Hypothesis 5

Performing the specifically designed exercise program is feasible, with high adherence over the time and well tolerated by the pregnant individuals.

Hypothesis 6

Performing the specifically designed exercise program is perceived as a good experience contributing to the fetal/neonatal and maternal health.

4 Objective of the study

MAIN OBJECTIVE

The main objective of this pilot study is to evaluate the impact of bed rest in terms of a) physiological parameters, b) mental health/emotional parameters and c) sleep cycle and quality of life parameters, in a group of bed rest hospitalized pregnant women. The parameters will then be compared depending on if they were included in a specifically designed exercise program (including resistance/strength exercises designed to be executed while in bed) or were followed by a standard management (not including an exercise program).

SECONDARY OBJECTIVES

To evaluate the recruitment rate in this type of study.
To evaluate the feasibility and adherence to the specifically designed exercise program.
To evaluate the satisfaction to be enrolled to the specifically designed exercise program.
To evaluate some trait-level psychological variables that could be mediating the effects of adherence and satisfaction of the program.

4.1 Main variables

- Exposure to the exercise program (yes/no)

- Physiological parameters
  - Time spent in moderate or vigorous activity (average per day).
  - Total physical activity (average per day in mG).
  - Handgrip strength test (score adjusted for gender and age).
  - Calf Circumference measurement (cm adjusted for gender and age).

- Mental health/emotional parameters
  - GAD-7
  - Perceived Stress Scale (PSS-10).
  - Edinburg Postpartum Depression Scale (EPDS) score and percentage of score ≥9.

- Sleep cycle and Quality of life parameters
  - Sleep average per night.
  - Insomnia Severity Index (ISI) score and percentage of score ≥8.
  - WHOQOL-BREF score.

- Feasibility evaluation of the implementation of the exercise program: time needed to recruit sample size, number of women who declined to participate in the study, number of women who give up participation in the study and adherence to the program (number of days of actual performance of the exercise program while admitted).

- Satisfaction evaluation regarding the exercise program: a questionnaire made specifically for the case evaluating different domains (length of the sessions, hardness of the sessions, daily repetition of the sessions, difficulty in particular exercises, willingness to repeat in case of re-admission, overall satisfaction to be included in the program), will be run to each individual.

4.2 Other variables

- Baseline Maternal and fetal characteristics at recruitment:
    - Evaluation of physical activity (GAQ-P questionnaire)
    - Maternal age
    - Maternal weight
    - Ethnic group (White/European, Hispanic/latin American, Black/African Americans, Arabic, Asian)
    - Gestational age at recruitment (weeks.days)
    - Twin pregnancy (yes/no)
    - Fetal growth percentile at admission (customized for gender and multiplicity)
    - Medical condition that justifies hospital admission (hypertensive disorders, preterm labor, rupture of membranes, antepartum bleeding, others).
    - Musculoskeletal limitations (injuries or pathologies).

- Maternal and fetal characteristics during hospital admission:
    - Medication while admitted (antihypertensive treatment, tocolysis, magnesium sulphate, antibiotics, corticosteroids, others)
    - Days in the intermediate care unit
    - Days of hospital admission
    - Fetal CTG (normal, suspicious, or pathological considering for gestational age and maternal medical condition).
    - Diet during the admission (Kcal, special needs)
    - Daily fluid intake
    - Other physiologic parameters:
        - Vitals: systolic and diastolic pressure, heart rate and temperature
        - Maternal weight
        - Percentage of time spent in inactivity, mild, moderate or vigorous activity and daily mean time (min) of activity.
        - Mean sleep period time, unstable sleep (low quality), sleep efficiency.
        - Blood and urine sampling including routine parameters: hemogram, glicosilated Hb, cardiovascular parameters including troponin, PIGF, NTproBNP and angiogenic factors, leukocytes, coagulation, lipid profile, liver and renal function, basic urine profile. Alkaline phosphatase (total and bone-specific), creatin kinase, osteocalcin and urinary N-terminal telopeptide will be also included.
        - Fetal hemodynamic parameters (measured by Doppler ultrasound) and maternal cardiovascular evaluation (measured by echocardiography: cardiac frequency, mean carotid thickness, subaortic integrated speed-time flow, heartbeat volume, left cardiac output, vascular resistance)
        - Step count
    - Other parameters measuring mental health/emotional state.
        - RRS questionnaire to measure ruminative response.
        - LOT (life orientation test) questionnaire to measure perception of self-control.
        - BFI-2- to measure negative emotionality trait.

- BDI-II to measure anhedonia.

- Perinatal outcomes
    - Gestational age at delivery
    - Birthweight and percentile
    - SGA/growth restriction classification, if any
    - Mode of delivery (spontaneous, assisted, cesarean section)
    - Composite adverse maternal outcome (yes/no considering any of the following: re-intervention, endometritis, infection of surgical wound, curettage, admission to intensive care unit, hysterectomy, need for transfusion, postpartum hemorrhage requiring medication other than oxytocin or ergometrine, maternal sepsis, death)
    - Neonatal admission to neonatal intensive care unit (yes/no)
    - Composite adverse neonatal outcome: (yes/no considering any of the following: respiratory morbidity – respiratory distress syndrome or transient tachypnea - requiring intubation, moderate-severe bronchopulmonary dysplasia, intraventricular hemorrhage grade III-IV, early-onset sepsis, periventricular leukomalacia, necrotizing enterocolitis, retinopathy requiring laser, fetal or neonatal death)
    - Breastfeeding rates at discharge and at 6 weeks follow-up

4.2 Description of methods and questionnaires

Specifically designed exercise program:

This will be an exercise program based on resistance/strength, specifically designed to be executed while in bed or minimal mobility. It is an adaptation from the exercise program described by Brun CR et al (Brun CR, Shoemaker JK, Bocking A, Hammond JA, Poole M, Mottola MF. Bed-rest exercise, activity restriction, and high-risk pregnancies: a feasibility study. *Applied Physiology, Nutrition, and Metabolism*. 2011;36(4):577-582).

Physiological parameters:

An **accelerometer Actigraph GT3X-BT** which will be worn by the individuals from recruitment to delivery or discharge from hospital. It will measure total daily mean time (min) of physical activity and percentage of daily time spent in inactivity, mild, moderate or vigorous activity. Also, mean sleep period time, unstable sleep (low quality), sleep efficiency and sleep average per night. Daily information will be retrieved.

Handgrip test: Grip strength is one of the physical fitness tests included in the Adult Eurofit Physical Fitness Test Battery (Eurofit for adults book: Assessment of Health Related Fitness, Council of Europe Publishing, 1995) which is a set of physical fitness tests covering a range of fitness components, designed for testing adults of Europe. Grip strength is usually measured using a hand-held dynamometer. The patient squeezes the dynamometer with all of their strength, typically three times with each hand. An average score is then calculated using the measurements from both hands (*Helen C et al, A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. Age Ageing (2011) 40 (4): 423-429*). It has been used also as a screening for sarcopenia (when <18 kg in females, *Chen LK at al, Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. J Am Med Dir Assoc. 2020 Mar;21(3):300-307.e2*).

Pre-test: Explain the test procedures to the subject. Prepare forms and record basic information such as age, height, body weight, gender, hand dominance. Calibrate dynamometer, adjust to suit

the subject.

Procedure: The subject holds the dynamometer in the hand to be tested, with the arm at right angles and the elbow by the side of the body. The handle of the dynamometer is adjusted if required - the base should rest on the first metacarpal (heel of palm), while the handle should rest on middle of the four fingers. When ready the subject squeezes the dynamometer with maximum isometric effort, which is maintained for about 5 seconds. No other body movement is allowed. The subject should be strongly encouraged to give a maximum effort.

Scoring: The best result from several trials for each hand is recorded, with at least 15 seconds recovery between each effort. The values listed below (in kg and lbs) give a guide to expected scores for adults.

Grip Strength Ratings for Females (in kg)

AGE	Weak	Normal	Strong
10-11	< 11.8	11.8-21.6	> 21.6
12-13	< 14.6	14.6-24.4	> 24.4
14-15	< 15.5	15.5-27.3	> 27.3
16-17	< 17.2	17.2-29.0	> 29.0
18-19	< 19.2	19.2-31.0	> 31.0
20-24	< 21.5	21.5-35.3	> 35.3
25-29	< 25.6	25.6-41.4	> 41.4
30-34	< 21.5	21.5-35.3	> 35.3
35-39	< 20.3	20.3-34.1	> 34.1
40-44	< 18.9	18.9-32.7	> 32.7
45-49	< 18.6	18.6-32.4	> 32.4

	MALES		FEMALES	
rating*	(lbs)	(kg)	(lbs)	(kg)
excellent	> 141	> 64	> 84	> 38
very good	123-141	56-64	75-84	34-38
above average	114-122	52-55	66-74	30-33
average	105-113	48-51	57-65	26-29
below average	96-104	44-47	49-56	23-25
poor	88-95	40-43	44-48	20-22
very poor	< 88	< 40	< 44	< 20

Calf Circumference measurement: AWGS'19 recommendations for sarcopenia screening includes the Calf Circumference measurement (*Chen LK at al, Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. J Am Med Dir Assoc. 2020 Mar;21(3):300-307.e2*). Although definition and diagnosis of sarcopenia are still evolving, sarcopenia has been defined as "age-related loss of muscle mass, plus low muscle strength, and/or low physical performance". Calf circumference provides information about normal muscle mass and overall can be a useful measure of an individual's overall health and fitness level. Indeed, it can reflect a decrease in muscle mass when limited physical activity. However, measurements may be affected by errors of interpretation due to the presence of edema and possible connective and adipose tissue in place of muscle tissue. In our study, we will be based on the anthropometric reference data from the CDC:

Procedure: To accurately measure calf circumference, use a flexible tape measure like a tailor's tape. Sit with your feet flat on the floor and wrap the measuring tape horizontally around your calf, moving it up and down to find the widest point: the horizontal circumference around the thickest part of the lower legs must be measured.

Scoring:

Table 34. Maximal calf circumference in centimeters for females 20 years of age and older by race and ethnicity and age, by mean, standard error of the mean, and selected percentiles: United States 2003–2006

Race and ethnicity and age	Number examined	Mean	Standard error	Percentile								
				5th	10th	15th	25th	50th	75th	85th	90th	95th
All race and ethnicity groups[1]				Centimeters								
20 years and over	4,133	38.3	0.13	31.8	33.0	33.8	35.0	37.5	40.9	43.0	44.7	47.1
20–29 years	676	37.8	0.25	31.5	32.4	33.1	34.5	37.1	40.2	41.9	43.7	46.6
30–39 years	648	38.7	0.23	32.2	33.6	34.1	35.3	38.0	41.2	43.4	45.3	47.2
40–49 years	765	39.2	0.27	32.8	33.8	34.6	35.7	38.5	42.1	44.2	45.6	47.8
50–59 years	578	38.7	0.24	32.3	33.4	34.3	35.5	37.7	41.3	43.1	44.3	47.4
60–69 years	673	38.5	0.30	31.5	32.6	33.6	35.2	37.6	41.1	43.1	44.6	47.2
70–79 years	437	36.8	0.27	31.1	32.1	32.9	33.9	36.2	39.0	40.6	42.0	44.7
80 years and over	356	35.5	0.19	29.8	30.8	31.7	33.1	35.4	37.7	38.7	39.8	41.4

From *McDowell MA, Fryar CD, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States, 2003–2006. National health statistics reports; no 10. Hyattsville, MD: National Center for Health Statistics. 2008. Available from: http://www.cdc.gov/nchs/data/nhsr/nhsr010.pdf.*

Get Active questionnaire for pregnancy (GAQ-P) (https://csep.ca/2021/05/27/get-active-questionnaire-for-pregnancy/) is a self-evaluation questionnaire of physical activity endorsed by the Canadian Society for Exercise Physiology (CSEP). The questionnaire, self-classifies how often and for how long she is engaged in physical activity of a light, moderate or vigorous intensity. Also, it addresses the question whether the woman should speak to her Obstetric Health Care Provider before beginning or continue to be physically active.

Questionnaires to evaluate mental/emotional health:

Mental/emotional health parameters: As main variables, three gold standard self-reported mental health questionnaires will be administered at baseline (w0), and afterwards every 2 weeks until discharge or delivery in order to have an estimate of the impact of bed rest and the PA program on the mental functioning of patients. We expect to observe an amelioration in anxiety, perceived stress and depression scores along the completion of the program. Parallelly, a brief visual evaluation of mood will be self-administered daily in order to have a pattern of emotional fluctuation along the completion of the exercise program. Next, we specified the psychological measurement instruments.

GAD-7: The generalized anxiety disorder assessment is a 7-item validated measurement scale that captures severity of anxiety symptoms. GAD-7 was originally used to identify General Anxiety Disorder according to DSM diagnostic criteria. However, it has also been extensively utilized as a dimensional measure of anxiety in different populations. Items are rated by means of a 4-point Likert Scale exploring frequency of the behavior worded in the item during the last 2 weeks. Total scores range from 0 to 21 with higher results indicating higher severity of anxiety.

PSS-10: the Perceived Stress Scale is a 10-item test to evaluate stress perceived which will be administered along with the anxiety and depression measures. The 10-item Perceived Stress Scale (PSS) is an instrument used to evaluate the degree to which a given life situation can be appraised as stressful. Originally, PSS was designed to appraise the level of stress during the last month therefore to meet our objective, PSS-10 instructions will be modified to cover explicitly the level of stress during the last two weeks. Responses are rated with a 5-point Likert scale with higher scores indicating severity of perceived stress and alterations at a cognitive and affective level.

EPDS: The Edinburgh Postnatal Depression Scale is a 10-item questionnaire considered a gold-standard for identifying depression and emotional distress in the perinatal period. In Spanish speaking populations, a cutoff point of 10 indicates risk of

developing depression and a further need of clinical assessment and score ≥13 or answering item 10 positive, indicates high risk. Patients must rate the 10 items by means of a 4-point Likert scale. Total scores range from 0 to 30 with higher total indicating more intense emotional distress.

SAM: The Self-Assessment Manikin is a visual standardized measure of emotional tone that covers 3 different affective domains (valence, arousal and sense of control). Completion requires less that 20 seconds and is highly suitable for individuals during hospital admission and bedrest. It can be used in many different contexts and the non-verbal design allows its usage with handicapped or children populations. MAS presents a series of manikin pictures representing different intensities of the 3 affective domains. Responses are made by selecting the manikin that best represents the emotional state of the patient. The patient selection is afterwards converted into a numerical result with higher scores indicating more positive affective tone.

Trait-Level variables:

These are a set of further psychological trait-level parameters: the next questionnaires will be administered once at w0. They are intended to measure stable characteristics of the person that we estimate will mediate the adherence, satisfaction and positive health impact of the exercise intervention.

RRS: The Ruminative Response Scale is a 10-item questionnaire intended to measure rumination, tendency to worriedness and repetitive thinking in front of stressful situations. It reflects a personality tendency considered a vulnerability trait for developing of common mental health conditions. Reponses are rated on a 4-point Likert scale. Higher scores indicate a higher tendency to ruminate and represent a vulnerability trait to psychological distress. Total responses range from 10 to 40.

LOT: The Life orientation test is a 10-item self-rated instrument measuring how optimistic a person feels about the future. High scores in optimism have been robustly associated to healthier behaviors protecting against cardiovascular diseases among other pathologies. It is a dimensional continuous measure describing a permanent trait of the person. Items are rated using a 5-point Likert scale. Total scores range from 0 to 40.

BFI-2: The negative emotionality trait will be evaluated at the beginning of the study to identify those individuals with proneness to negative thinking. This 6 -item brief personality questionnaire reflecting a scale of neuroticism will be administered. Responses are made by using a 6-point Likert scale, with higher scores indicating higher levels of negative thinking.

BDI-II: BDI-II is a questionnaire measuring depression at a cognitive, affective and behavioral level. For the present study only 4 items related to hedonic experience will be selected. Higher scores in each item indicate severity in the loss of hedonic capacity. Reponses are made by using a 4-point Likert scale.

<u>Questionnaires to evaluate quality of sleep and quality of life:</u>

Sleep average per night will be measured using the **Actigraph GT3X-BT**.

Quality of sleep will be evaluated using the Spanish version of the **Insomnia Severity Index (ISI)** which is composed of seven items that evaluate the severity of sleep disturbance during the past 2 weeks. Each item is rated on a five-point Likert scale and

the total score indicates the severity of insomnia. Score 8-14 is mild and 15 or more moderate to severe insomnia), impact on daily life and treatment response.

Quality of life will be evaluated using the Spanish version of the **WHOQOL-BREF** which assesses 4 domains of quality of life regarding the last two weeks: physical health, psychological health, social relationships, and environment. physical health (7 items), psychological health (6 items), social relationships (3 items), and environmental health (8 items); it also contains QOL and general health items. Each individual item of the WHOQOL-BREF is scored from 1 to 5 on a response scale, which is stipulated as a five-point ordinal scale. The scores are then transformed linearly to a 0–100-scale. There is not a standard cut-off proposed but the higher the score, the higher the quality of life.

5 Study design

Given the scarce information about the variables proposed in these kind of subjects (pregnant people with complications and hospitalized in almost complete bedrest, we will follow a two-step study:

We will conduct a **pilot** randomized controlled study including pregnant women admitted to the Maternal Intermediate Care Unit in the Maternal-Fetal Medicine Department of the Hospital Clinic. Two groups of pregnant women will be studied depending on the exposure to the specific designed exercise program:

No-exercise group (NEG): women admitted in the Maternal Intermediate Care Unit who will follow the standard management for its complication.

Exercise group (EG): women admitted in the Maternal Intermediate Care Unit who will follow the standard management for its complication and will follow a specific designed exercise program.

The abovementioned variables will be evaluated, and dimension of differences considered. If appropriate, a focus-group will be designed in order to determine clinical relevant variables and differences and its effect-size to assess future sample-size calculations.

A **full** RCT study will be designed and conducted in a second-step with an appropriate sample size to evaluate the key variables selected considering the recruitment rate and other findings extracted from the pilot study.

6 Participants selection

Pregnant women admitted in the Maternal Intermediate Care Unit who have remained stable of her complication after 24-48h of admission will be approached by the investigators to participate in the study. If informed consent form signed, they will be randomized and included in the no-exercise group or exercise group:

6.1 Inclusion criteria

Maternal age of 18 or more
Delivery not expected within 1 week after recruitment.
Language ability to understand the study.
Informed consent signed.

6.2 Exclusion criteria

Fetal death
Severe mental health disorders and substance abuse disorders.

7 Treatment or development of the study

Role of the investigators:

MP and EFV-B designed the study because their expertise in clinical Maternal-fetal Medicine and Sports Medicine, respectively. FM and FF provided assessment in the study design. RB provided assessment to the exercise program because of his expertise in physical activity; AM and XS provided assessment on the emotional/psychological field and will run the evaluation in this area; GR provided assessment because of his expertise in Sports Medicine.

MP will be supervising the clinical management. MP, FM, FF, AJ and EG will participate to evaluate eligibility and recruitment of the participants. EFV-B and SE will be supervising the exercise program execution. EFV-B, SE, EG and AJ will be in charge to explain the exercise program to participants and will evaluate its adherence or barriers to develop the program. MP, FM, FF, AJ, EG, AM and XS will retrieve clinical information from clinical files when needed.

All investigators participated, reviewed, and approved the proposal and development of the study.

Vital parameters:

Systolic and diastolic pressure, heart rate and temperature will be taken as part of the routine management, three times a day (8:00±2h, 16:00±2h, 24:00±2h) until delivery or discharge. No additional measurements will be taken because of this study.

Blood sampling parameters, fetal hemodynamic parameters and maternal echocardiographic parameters will be measured at wk0 (recruitment), wk1±2d, wk2±2d, wk3±2d, and weekly until delivery, following routine care. No additional blood sampling will be carried out because of this study but alkaline phosphatase (total and bone-specific), creatin kinase, osteocalcin and urinary N-terminal telopeptide, glicosilated Hb, cardiovascular parameters including troponin, sFlt-1, PIGF, NTproBNP, will be added to the routine analysis.

An accelerometer Actigraph GT3X-BT will be worn by the individuals from recruitment to delivery or discharge from hospital. It will measure daily mean time (min) of activity and percentage of daily time spent in inactivity, mild, moderate or vigorous activity. Also, mean sleep period time, unstable sleep (low quality), sleep efficiency and sleep average per night. Daily information will be retrieved.

Participants included in the exercise group will be trained to execute once daily (estimated duration 30 minutes) the specifically designed exercise program by investigators specialists in Sports Medicine and in Physiotherapy. Midwives in charge of the maternal-fetal unit will be running the follow up. Investigators specialist in Maternal-fetal medicine will be in charge of the clinical management and decisions.

Validated Spanish versions of the questionnaires evaluating mental/emotional health and quality of sleep and life will be used. Investigators specialized in psychology will be in charge of this part. The three gold-standard self-reported mental health questionnaires will be run at wk0, wk2+/-2d and then every 2 weeks until discharge or delivery and at 6+/-1 weeks postpartum. The SAM questionnaire will be run daily. Questionnaires measuring psychological trait-level parameters will be run once at wk0. Quality of sleep and life questionnaires will be run at wk0, wk2+/-2d and then every 2 weeks until discharge or delivery.

CHRONOGRAM IN THE NO-EXERCISE/EXERCISE GROUPS

w0

No-exercise group	Exercise group
Maternal and fetal baseline characteristics	Maternal and fetal baseline characteristics
Blood sampling and fetal/maternal workout	Blood sampling and fetal/maternal workout
Mental/emotional health evaluation	Mental/emotional health evaluation
Trait level parameters evaluation	Trait level parameters evaluation
Sleep and quality of life evaluation	Sleep and quality of life evaluation
Actigraph activation	Actigraph activation
	Training in the Exercise Program: 30 minutes daily

w0+3d and every wN +3d until discharge or delivery whichever occurs first.

No-exercise group	Exercise group
Maternal and fetal standard management	Maternal and fetal standard management
	Checking follow up of Exercise Program

Daily

No-exercise group	Exercise group
SAM questionnaire	SAM questionnaire

w1

No-exercise group	Exercise group
Blood sampling and fetal/maternal workout	Blood sampling and fetal/maternal workout
Maternal and fetal standard management	Maternal and fetal standard management
Actigraph retrieval of information	Actigraph retrieval of information
	Checking follow up of Exercise Program

w2

No-exercise group	Exercise group
Blood sampling and fetal/maternal workout	Blood sampling and fetal/maternal workout
Mental/emotional health evaluation	Mental/emotional health evaluation
Sleep and quality of life evaluation	Sleep and quality of life evaluation
Actigraph retrieval of information	Actigraph retrieval of information
	Checking follow up of Exercise Program

w3, w5 and odd weeks of follow up until discharge or delivery whichever occurs first.

As in w1

w4, w6 and even weeks of follow up until discharge or delivery whichever occurs first.

As in w2

Delivery

No-exercise group	Exercise group
Perinatal outcomes	Perinatal outcomes
Mental/emotional health evaluation (if even week)	Mental/emotional health evaluation (if even week)
Sleep and quality of life evaluation (if even week)	Sleep and quality of life evaluation (if even week)
Actigraph retrieval of information	Actigraph retrieval of information
	Feasibility information about Exercise Program
	Satisfaction information about Exercise Program

6 weeks postpartum

No-exercise group	Exercise group
Mental/emotional health evaluation	Mental/emotional health evaluation
Blood sampling and fetal/maternal workout	Blood sampling and fetal/maternal workout
Postpartum and mental/emotional health evaluation	Postpartum and mental/emotional health evaluation

8 Statistical analyses

8.1 Sample size

As a first step, this is a pilot study planned to evaluate dimension of differences in this clinical context. Potential recruitment, adherence and feasibility of a regular exercise program in this context will be evaluated. For this first step we plan to include 10 women in the no-exercise group (NEG) and 10 women in the exercise group (EG).

Variables proposed will be evaluated and dimension of differences considered. If appropriate, a focus-group will be designed in order to determine relevant clinical differences. Finally, effect-size to assess sample-size calculations will be used to design the second step of the study.

A RCT study with the appropriate sample size to evaluate key variables and considering the recruitment rate and other findings extracted from the pilot study will be conducted on subjects with the same inclusion/exclusion criteria described.

8.2 Statistical analysis

As a general rule, qualitative variables will be described as absolute frequencies and relative percentages and quantitative variables as means and medians for the assessment of central tendency and SD and IQR for the assessment of dispersion. Univariate analysis: for the comparison of two qualitative variables, the $\chi 2$ test or Fisher's exact test will be used. When the variables are quantitative, Student's t-test for independent samples or the Mann-Whitney U test will be used if the applicability criteria are not met. For statistical analysis, values of $p<0.05$ will be considered as statistically significant. The data will be analyzed with the SPSS software (V.20.0, IBM or newer).

The randomization of participants will be conducted using a simple randomization method to ensure an equal and unbiased distribution between the treatment and control groups. A pseudorandom number generator will be utilized to create the randomization list. This list will be generated using specialized software to assign participants to either the treatment group or the control group in a 1:1 ratio. To maintain the integrity and confidentiality of the randomization process, the randomization list will be securely administered by the study sponsor. It will be stored in a password-protected file accessible only to authorized personnel. This approach ensures that the randomization process remains blinded and reduces the risk of allocation bias.

9 Ethics

The study will be carried out in compliance with the Declaration of Helsinki (current version; currently Fortaleza, Brazil, October 2013) and in accordance with the protocol and legal requirements expressed in Law 14/2007 of July 3, on Biomedical Research.

Informed consent will be requested from patients before inclusion in the study. Consent from both parents will be obtained to be able to use the clinical information of the fetus/newborn.

10 Data management plan.

Data will not be reused from other studies as there is no available data of this characteristics. All data of this study will be codified and collected in a dedicated database based on the REDCap® platform hosted in the Coordinating center (Hospital Clínic). This database will have limited access through username and password of authorized personnel. The coding table will be kept password-protected and under the supervision of the sponsor.

Personal characteristics, information about pregnancy complications, delivery, cesarean section rate, neonatal adverse outcomes, maternal morbidity and hospital stay will be collected for all women included in the trial, independently on their group. Effort will be made to follow FAIR principles (Findable, Accessible, Interoperable and Reusable).

Researchers who access this database will be responsible for the confidentiality of the data collected. In this database, a code will be assigned to each case to enter the other variables in a database without any information that can identify the patient or study subject. These measures are intended to ensure compliance with the provisions of Organic Law 3/2018, of 5 December, on the Protection of Personal Data and the guarantee of digital rights.

Data analysis will be managed from investigators from the Coordinating center who will be also the ones to carry out clinical interpretation of the data analysis.

11 Data processing and data file. Data confidentiality.

The data will be collected in a REDCap® database specifically designed for the study that will be kept by the researchers. The data will later be extracted and analyzed to obtain results.

The processing, communication and transfer of personal data of all participants will comply with EU Regulation 2016/679 of the European Parliament and of the Council of April 27, 2016 regarding the protection of natural persons regarding to the processing of personal data and the free circulation of data, and to Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights. The legal basis that justifies the processing of your data is the consent you give in this act, in accordance with the provisions of article 9 of EU Regulation 2016/679.

The data for these studies will be collected only identified by a code, so no type of information that allows identifying the participants will be included. Only the study doctor and his collaborators with the right of access to the source data (medical history) will be able to relate the data collected in the study with the patient's medical history.

The identity of the participants will not be accessible to any other person except in a medical emergency or legal requirement.

The health authorities, the Research Ethics Committee and personnel authorized by the study promoter may have access to the identified personal information, when necessary to verify data and procedures of the study, but always maintaining confidentiality in accordance with current legislation.

Only the encrypted data will be transferred to third parties and other countries, which in no case will contain information that can identify the participant directly (such as name and surname, initials, address, social security number, etc.). In the event that this transfer occurs, it would be for the same purpose of the study described and guaranteeing confidentiality.

If a transfer of encrypted data is carried out outside the EU, either in entities related to the hospital center where the patient participates, to service providers or to researchers who collaborate with us, the participants' data will be protected by safeguards such as contracts or other mechanisms established by data protection authorities.

As promoters of the project, we undertake to process the data in accordance with EU Regulation 2016/679 and, therefore, to maintain a record of the processing activities that we carry out and to carry out a risk assessment of the treatments that we carry out. , to know what measures we will have to apply and how to do it.

In addition to the rights already contemplated by the previous legislation (access, modification, opposition and cancellation of data, deletion in the new Regulation) participants can now also limit the processing of data collected for the project that is incorrect, request a copy or transferred to a third party (portability). To exercise these rights, you must contact the principal investigator of the study or the Data Protection Delegate of the Hospital Clínic of Barcelona through protecciodades@clinic.cat. You also have the right to contact the Data Protection Agency if you are not satisfied. to.

Data cannot be deleted, even if a patient drops out of the study, to ensure the validity of the research and to comply with legal duties and drug authorization requirements.

The Researcher and the Sponsor are obliged to retain the data collected for the study for at least 5 years after its completion. Subsequently, personal information will only be retained by the health care center and by the sponsor for other scientific research purposes if the patient has given consent to do so, and if permitted by applicable law and ethical requirements.

12 Management of biological samples

For this pilot study no samples will be stored

13 Funding

There is no specific financial support for this study. All interventions and measurements will be carried out in the context of the clinical management.

14 Publication policy

This is a pilot study and findings are to be evaluated. As well feasibility of the study has yet to be determined. Depending on the quality of data, investigators will take care for results from this study being published in peer-reviewed journals.