Exercise training in women with unexplained recurrent pregnancy loss to optimize receptive endometrial NK cell population and function

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Is moderate exercise training for 12 weeks in women with RPL improving CD56bright eNK cell population and function?

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55979

Source
ToetsingOnline

Brief title
HMove

Condition

- Other condition
- Abortions and stillbirth

Synonym
recurrent miscarriage, Recurrent pregnancy losses

Health condition

reproductieve immunologie

Research involving

Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Exercise training, NK cells, Recurrent pregnancy losses, Reproductive immunology

Outcome measures

Primary outcome

CD56bright NK cell population and function in endometrium and peripheral blood

in women with reduced endometrial NK cells (<80%).

Secondary outcome

Frequency and function of (CD56bright) eNK cells compared to baseline in women

with unexplained RPL and more than 80% of eNK cells. General immune assessment

of all samples (<80% and >80% eNK cells) for peripheral NK cells (before and

after 12 weeks of an aerobe exercise intervention) and endometrial NK cells

(before, during and after 12 weeks of an aerobe exercise intervention) in the

intervention group and time control group. Additional to the immunological

effects we will study the effects of exercise training on the vaginal

microbiota, on cardiovascular and metabolic parameters, on autonomic balance,

on uterine blood flow and on physical fitness levels. One year after completion

of the intervention, pregnancy rate and live birth rate will be assessed.

Study description

Background summary

Recurrent pregnancy loss (RPL) is defined as two or more miscarriages, which is the case in 1-2%. Still, in 50-75% of the couples no underlying condition is found and leaves clinicians without means to treat these women to prevent recurrent losses. It has been suggested that inadequate adaptation of the maternal immune system is responsible for a proportion of these unexplained losses. The composition of the uterine immune cell population is unique as compared to other mucosal sites as it has to tolerate the presence of a semi-allogenic fetus, while at the same time providing sufficient plasticity to counter infectious threats.

In the mid-secretory phase endometrial NK cells (eNK) rapidly increase. In early pregnancy, approximately 80% of decidual leukocytes are eNK cells, compared to 5-15% in peripheral blood. These eNK cells express high levels of CD56 (CD56bright NK cells), in contrast to peripheral NK cells (CD56dim NK cells). The CD56bright NK cells have a more immunomodulatory function, with the ability to secrete cytokines. This immunomodulatory capacity of eNK cells suggests that they play a crucial role in embryo implantation and development of the trophoblast. Recent meta-analysis showed an increased number of peripheral NK cells in women with RPL, however no difference was seen in eNK cells. For research purposes taking biopsies from endometrial tissue is a very invasive and painful procedure, that limits its feasibility in the routine investigations for RPL. Instead of using eNK cells, NK cells isolated from menstrual blood are a good source for eNK cells.The yield of lymphocytes after collection of menstrual blood is even much higher than with endometrial biopsies, and menstrual NK cells closely resemble biopsy-derived eNK cells.

In a pilot study we found that 6 out of 19 women with unexplained RPL (32%) had less than 80% CD56bright NK cells derived from menstrual blood compared with none of the women with a normal pregnancy, sensitivity and specificity of 72% and 100%. The lower numbers of CD56bright NK cells suggest that this may be a possible cause, in a subgroup of women with RPL, for their losses.

Exercise seems an effective intervention to improve the immune system, more and more evidence in cancer research shows that exercise improves outcome in patients. Exercise promotes healthy reproduction by reducing the risk on preeclampsia and gestational diabetes. In women with RPL conflicting results have been found on the effect of exercise and no studies investigate the impact of exercise on the chances of a live birth. In addition, the effect of exercise on eNK cell population has never been studied. NK cells are the most responsive immune cells to exercise, displaying an activation and acute mobilization to the circulation during physical exertion. Moderate training showed the highest increase in peripheral NK cell counts. We observed in earlier studies that women with RPL have a reduced physical fitness (unpublished data). We did not study yet whether there was a direct relation with the altered NK cell phenotypes that we observed.

Study objective

Is moderate exercise training for 12 weeks in women with RPL improving CD56bright eNK cell population and function?

Study design

Interventional study

Intervention

Exercise training for 12 weeks.

Study burden and risks

After inclusion, a questionnaire will be taken once (CRF, SQUASH). Blood collection, a vaginal internal examination (ultrasound, swap) and a cardiovascular screening (blood pressure measurement, height, weight, analysis). autonomic nervous system) will be performed twice (once before and once after the intervention). Women will also twice undergo an exercise test by means of a maximal bicycle test. During the intervention, they will follow a sports program (bike trainings) for 3 months at a gym in their own area (weeks 1-6 2x a week 60 minutes and weeks 7-12 3x a week 60 minutes). They will then be called weekly to evaluate the sports intervention and also to motivate the participants. In addition, menstrual blood will be collected four times (once before, twice during and once after the intervention). 12 months after the end of the intervention, women will be sent a short questionnaire once more as a follow-up to analyze the pregnancy outcomes. The risk for the subjects associated with this study is minimal. We kept the invasiveness of our study protocol to a minimum see also study protocol section 9.3.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Women with two or more unexplained pregnancy losses, defined as women without uterine abnormalities, antiphospholipid syndrome, thyroid abnormalities and abnormal parental karyotyping if indicated according to international guideline.
Couples should not be aiming to conceive during the time course of the exercise intervention.

Exclusion criteria

-Age above 40 years
-Use of immunosuppressive drugs, biological or antidepressants
-Use of hormone conceptive
-HIV positivity
-Current or recent (<2 weeks) symptomatic genital infection such as chlamydia, gonorroa, or pelvic inflammatory disease
-Pre-existent diabetes mellitus, autoimmune disease or overt cardiovascular disease
-Smoking or use of medication or supplements that might affect the cardiovascular system
-Vaccination (i.e Covid) within 3 months prior to or during sampling and intervention
-New pregnancy at time of measurements, breastfeeding
-Current or recent (<3 months ago) pregnancy
-Women with plans to become pregnant during the course of intervention
-(Physical) inabilities to follow moderate aerobe cycling training

-Participants who are not capable of signing the informed consent

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-03-2022
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	19-10-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-10-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL77307.091.21