WESTERN SYDNEY
UNIVERSITY

Participant Information Sheet

Women with diminished ovarian reserve

Project Title: *Effectiveness of adjunct naturopathy for pregnancy rates in women with diminished ovarian reserve compared to usual care alone: feasibility of a randomised controlled trial*

Project Summary:

This is a preliminary study which will provide information on whether it is possible to conduct a larger clinical trial on naturopathy for pregnancy rates in women with diminished ovarian reserve (DOR).

You are invited to participate in a research study being conducted as part of a PhD project of Ms Alison Maunder under the supervision of Dr Carolyn Ee, Dr Mike Armour, Dr Susan Arentz at the NICM Health Research Institute at Western Sydney University and Dr Michael Costello at the School of Women's and Children's Health at University of NSW. It has Ethics approval (H14745 February 2022).

How is the study being paid for?

The Jacka Foundation of Natural Therapies has provided funds for this study. Ms Maunder's position as a PhD candidate is supported by a scholarship from the Jacka Foundation of Natural Therapies.

Why is this study being done?

In Australia, one in six couples will have difficulty conceiving a baby. Diminished ovarian reserve (DOR) is a risk factor for pregnancy. It is diagnosed if women have regular periods but there are fewer eggs remaining in the ovaries than other women of the same age. The best way to help women with DOR is unclear as there are few helpful treatments available.

Many women in Australia use naturopathy to improve their chances of having a live healthy baby. However, the current research on naturopathy is insufficient in telling us whether or not it is an effective and safe treatment for women with DOR. We are interested in the possible role of naturopathy as an additional treatment to increase pregnancy rates in women with DOR. To answer this question, we will need to conduct a larger clinical trial.

Prior to embarking on such a large and expensive study, we want to do a small, preliminary study to see if naturopathy may be effective, whether it is possible (feasible) to conduct a larger study, and whether our proposed treatment is acceptable to women with DOR. We have completed a survey with women with DOR which has informed the design of this study.

What will I be asked to do?

In summary: After initial assessment and consent, you will be asked to provide documentation of your DOR diagnosis and to have a blood test for safety checks (blood count, liver and kidney function). Once this is complete and if you are eligible, you will be asked to complete surveys about your health. Once complete, you will be enrolled in the study and allocated to either the intervention group or control group (50:50 chance). Both groups will record the first day, length and flow of each menstrual period and test for pregnancy each menstrual cycle. Each week, you will fill in a short online diary to check progress.
In the intervention group – you will:

- Attend four naturopathic consultations about 4-5 weeks apart.

- Take nutritional supplements and herbal medicines each day.

In the control group – you will:

- Take nutritional supplements (two tablets) each day.
- Phone call at midpoint (Week 8) with a researcher.

At the end of the four months, you will have another blood test for safety checks (your blood count, liver and kidney function), complete surveys about your health and satisfaction with the trial. Apart from the blood tests, all measurements are either done online, over the phone or by return post.

In more detail:

- Screening (15 minutes): provide de-identified documentation of your DOR diagnosis and to have a blood test taken for safety checks at a pathology laboratory located near you. Eligibility will require blood assessments to be in the normal range.
- Baseline (40 minutes): if eligible, you will be asked to complete three online questionnaires about you (demographics), about your reproductive history, mental health, quality of life, lifestyle and body measurements. Once completed, you will be randomly allocated in 1:1 ratio to either the intervention group or control group.
    In the intervention group – the research team will:
    - Book an appointment for your first naturopathic consultation (face-to-face or telehealth)

    In the control group – the research team will:
    - Book an appointment for midpoint (Week 8) telephone call with the researcher
    - Organise for 8-weeks' worth of study products and pregnancy test kits to be delivered to your home address (or your preferred location) where you will start to take the study medication as per the instructions given to you from the research team
- Intervention group (225 minutes)
    - Attend four naturopathic consultations about 4-5 weeks apart (initial 75 minutes, follow-up 45 minutes each, total: 210 minutes or 3.5 hours)
    - Following each naturopathic consultation, study products will be delivered to your home address (or your preferred location) where you will start to take the study medication as per the instructions given to you from your naturopath; pregnancy test kits will be included in the first delivery.
    - Take nutritional supplements and herbal medicines each day.
    - Record the first day and length of each menstrual period for 16-weeks in a menstrual calendar
    - Test for pregnancy each menstrual cycle (2-3 minutes per day at start of menstrual cycle)
    - Complete an online diary once per week to check your progress (2 minutes)
- Control group (45 minutes)
    - Take nutritional supplements each day.
    - Record the first day, length and flow heaviness of each menstrual period for 16-weeks in a menstrual calendar
    - Test for pregnancy each menstrual cycle (2-3 minutes per day at start of menstrual cycle or as needed)
    - Complete an online diary once per week to check your progress (2 minutes)
    - Phone call at midpoint (Week 8) (30 minutes) – the research team will call you to check on your progress in the study, the study products and any side-effects you may have experienced
- End of treatment (50 minutes): you will be asked to have a blood test taken for safety checks (blood count, liver and kidney function) and complete two online questionnaires. The first is the same as at baseline (mental health, quality of life, lifestyle and body measurements and

the second is a participant satisfaction questionnaire. On the completion of these measurements, you will be reimbursed for your time by way of a $50 gift voucher.

- Post-treatment follow-up (5 minutes): this will just be a short phone call to check if you experienced any delayed side effects after finishing the treatment period for the study.
- Post-study follow-up (10 minutes): this will just be a short phone call to check if you have fallen pregnant 3-months after the trial, and if you are pregnant, 1-month after your estimated date of delivery to check on your progress.

How much of my time will I need to give?

The total time you will need to give in this study is approximately (not including travel time to pathology centre) that is spread across 4-months

- Intervention group: 5-6 hours
- Control group: 2-3 hours

What is naturopathy?

If you agree to take part in the study, you will have a 1 in 2 chance of being randomly allocated to receive the naturopathic intervention.

Naturopathy is a distinct system of traditional, complementary and integrative medicine (TCIM) with origins in Europe and America that is based on six principles of practice: “first do no harm”, support the healing power of nature, treat the fundamental cause of illness, treat the whole person, educate on healthy living and preventative care. A fundamental belief of naturopathy is that ill health begins with a loss of vitality. The vital force can be diminished by a range of physical, mental, emotional, spiritual and environmental factors. Health is restored by raising the vitality and initiating the regenerative capacity for self-healing, and the processes of metabolism, growth and reproduction.

Naturopathy is a complex intervention and common treatments used in the management of women with infertility include counselling, education, self-detection of ovulation signs and symptoms and lifestyle interventions including diet, exercise, stress-reducing behavioural practices and targeted nutritional supplements and herbal medicines prescribed according to the needs of individuals. The overarching aim is to improve general health and wellbeing and to minimise the negative impact of infertility and to increase the chances of pregnancy and a live healthy baby.

Who will provide the naturopathic treatments?

We have selected experienced naturopaths that have a Bachelor degree in Naturopathy, have five or more years of clinical experience and are registered with a naturopathic association that is recognised by the World Naturopathic Federation. These naturopaths have received additional training from Alison Maunder on providing naturopathy for the trial. You may choose your naturopath from our list of selected and trained practitioners who have been engaged to provide treatments for this study.

What is usual care?

Both groups will continue with usual care as provided by their reproductive health and medical teams. All medications required as part of a participant’s normal clinical care for co-morbid conditions are permitted during the trial. Participants will be advised of publicly available lifestyle advice provided on the ‘Your Fertility’ website https://www.yourfertility.org.au/

During this trial, usual care will not include naturopathy.

What benefits will I, and/or the broader community, receive for participating?

You may benefit from participating in this study in several ways:

- You will receive nutritional supplements to support pregnancy for 16-weeks.
- You will receive pregnancy test strips to check for pregnancy.
- You will have a blood test for safety monitoring (to ensure there is no pre-existing and unidentified issues with your liver or kidney function)
- Once you have completed your end of intervention procedures, you will be reimbursed for your time by way of a $50 Woolworths voucher.
- You may experience benefits from naturopathic care for achieving pregnancy.

The benefits to the broader community will not be realised for some time yet, but if naturopathy is shown to be beneficial, you will be helping to advance medical research, which could assist in the understanding of effective treatments for women with DOR in the future.

Where will I get the safety blood tests taken and what are the risks?

Blood tests are taken by qualified collection staff at your local Laverty Pathology (or sister companies depending on region). You'll need to take your pathology test request form as supplied by the research team. You will not be required to fast. Make sure you drink plenty of water prior to your pathology testing - unless your GP has given you a reason not to. This makes it easier to conduct your blood test. Smoking is not permitted on the day of the test and until the test is completed.
On arrival at your chosen collection centre, a blood sample will be taken from you by one of Laverty's trained collecting staff. You are recommended to leave the dressing strip in place, avoid tight clothing on the arm and avoid heavy lifting for 1-3 hours. Blood tests are usually well-tolerated, however some people may experience minor pain or discomfort, bleeding, swelling or bruising. Contact your GP if symptoms persist.

Will the study involve any risk or discomfort for me? If so, what will be done to rectify it?

The nutritional supplements and herbal medicines used in this study have all been pre-evaluated for safety and permitted for inclusion in oral medicines in Australia.

The **nutritional supplements** are considered relatively safe for general adult use and during pregnancy with no drug related serious adverse events expected at the prescribed dose. Side effects are expected to be infrequent, and mostly mild to moderate in severity. You may experience: nausea, vomiting, stomach discomfort or pain, diarrhoea, loss of appetite, bad breath, metallic taste, heartburn, flatulence, dry mouth, mouth irritation, headache, dizziness. Gastrointestinal side effects may be minimized if taken with meals. Do not exceed the prescribed dose of the nutritional supplements. If you miss a dose, skip the dose you missed and take your next dose when you are meant to. Do not take a double dose to make up for the one missed. You should not take any other vitamin, mineral or nutritional supplement at the same time due to risk of excessive dosage.

The **herbal medicines** are considered relatively safe for general adult use with no drug related serious adverse events expected at the prescribed dose. However, during pregnancy there is insufficient reliable information about the safety of these herbal medicines; so you should stop the herbal medicines when you become pregnant (or test positive for pregnancy). You will not receive every herbal medicine; your naturopath will choose those that are appropriate for you. Side effects are expected to be infrequent, and mostly mild to moderate in severity. You may experience: breast tenderness, irregular menstruation, dizziness, nausea, vomiting, burping, flatulence, gastrointestinal upset, abdominal pain or discomfort, diarrhoea, constipation, fever, headache, irritability, skin irritation, mouth irritation, fatigue,

insomnia, weight gain, lack of appetite. Do not exceed the prescribed dose of the herbal medicine. If you miss a dose, skip the dose you missed and take your next dose when you are meant to. Do not take a double dose to make up for the one missed. You should not take any other herbal medicine at the same time due to risk of excessive dosage.

Chamomile should be avoided if you are allergic to chamomile, and caution is advised if you have a known sensitivity to plants in the daisy family. If you experience any symptoms of an allergy (trouble breathing, or swelling of the face, mouth, lips, gums, tongue or neck, rash, hives or blisters) you should stop using the herbal medicine, seek immediate medical attention and inform the research team as soon as possible.

In rare cases, other herbal medicines have been associated with serious side effects. Dong quai and licorice may increase blood pressure. Black cohosh and withania may be associated with liver injury. If you develop symptoms or signs of liver failure (yellowing of your skin and whites of the eyes/jaundice, pain in your upper right abdomen, abdominal swelling, nausea, vomiting, a general sense of feeling unwell (malaise), disorientation or confusion and sleepiness) you should stop using the herbal medicine, seek immediate medical attention and inform the research team as soon as possible.

Some herbal medicines may interact with Warfarin or other blood thinning medication; thyroid hormones, antidiabetic drugs, cholesterol lowering medications; blood pressure lowering medications; anti-psychotic drugs; benzodiazepines or anti-seizure medications so it is very important that you tell the naturopath if you are taking these types of medications. The naturopaths are experienced in prescribing nutritional supplements and herbal medicines and avoiding interactions with other medications. They will ask you about any new medications you might have started at each consultation. They will also monitor side effects.

Side Effects will be monitored for all participants through a weekly online diary, naturopaths will check with participants at each consultation, and the study staff will check for side effects in the control group through a phone call at midpoint (Week 8) and at endpoint (Week 16). All participants will also take another blood test at the end of the trial to compare to your blood results from before you started the study medication. Lastly, the study staff will check in on all participants via a phone call 2weeks after you stop taking the study medication to make sure you haven't had any delayed reactions.

If you have any side effects that you are concerned about at any time, even if you think they are mild, please contact the study staff via the contact details at the end of this sheet. If you feel they are serious or life threatening, please immediately seek medical attention from your GP or emergency department.

If this study raises any concerns or causes you to experience any discomfort, please contact Dr Ee, your GP, Lifeline phone 131114 or one of the following organisations that support women who have experienced pregnancy complications or difficulty falling pregnant:

ACCESS Australia https://access.org.au/

Pink elephants https://miscarriagesupport.org.au

How do you intend to publish or disseminate the results?

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that the participant cannot be identified. As the survey is collected anonymously, your responses will not be able to identify you at all.

Will the data and information that I have provided be disposed of?

Please be assured that only the researchers will have access to the raw data you provide. However, your data may be used in other related projects for an extended period of time.

In accordance with the Australian privacy and other relevant laws, you have the right to request access to your information that we have collected and stored by the research team. Please contact the clinical trial officer, Alison Maunder, alison.maunder@westernsydney.edu.au, 0417 800 355, if you would like access to your information.

We will store all information collected for this study securely and destroy it 15 years after the results are published in accordance with university policy and the Australian Code for the Responsible Conduct of Research.

Can I withdraw from the study?

Participation is entirely voluntary and you are not obliged to be involved. If you do participate, you can withdraw at any time.

If you choose to withdraw, the study investigator or other staff may ask you for your reason for withdrawing to ensure we follow up on any unresolved issues. Whatever your decision, it will not affect your medical treatment or your relationship with the medical or other staff involved in the study.

What happens to my data if I withdraw from the study?

If you withdraw from the study, the data you have already provided will remain in the study unless you specifically ask for it to be removed. All information collected for this study will be stored securely and destroyed 15 years after the results are published in accordance with university policy. In accordance with the relevant Australian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. Please contact the study team member named at the end of this document if you would like to access your information.

Can I tell other people about the study?

Yes, you can tell other people about the study by providing them with a link to the screening survey or Alison Maunder's (Clinical Trial Officer) details. They can then contact Alison Maunder to discuss their participation in the research project and obtain a copy of the information sheet.

What will happen with my information if I agree to it being used in projects other than this one?

The researchers are asking that you agree to supply your information (data) for use in this project and to also agree to allow the data to potentially be used in future research projects.

This request is in line with current University and government policy that encourages the re-use of data once it has been collected. Collecting information for research can be an inconvenience or burden for participants and has significant costs associated with it. Sharing your data with other researchers gives potential for others to reflect on the data and its findings, to re-use it with new insight, and increase understanding in this research area.

You have been asked to agree to extended consent.

What is extended consent?

When you agree to extended consent it means that you agree that your data, as part of a larger dataset (the information collected for this project) can be re-used in projects that are:

- an extension of this project
- closely related to this project
- in the same general area of this research.

The researchers will allow this data to be used by other researchers who wish to conduct research on naturopathy, infertility and/or diminished ovarian reserve.

To enable this re-use, your data will be held at the University in its data repository and managed under a Data Management Plan. The stored data available for re-use will not have information in it that makes you identifiable. The re-use of the data will only be allowed after an ethics committee has agreed that the new use of the data meets the requirements of ethics review.

The researchers want to keep the data for a significant period of time (in excess of 15 years) for possible re-use – until it is felt that it is no longer needed for research. After this time the data will be securely destroyed.

You are welcome to discuss these issues further with the researchers before deciding if you agree. You can also find more information about the re-use of data in research in the National Statement on Ethical Conduct in Human Research – see Sections 2.2.14 - 2.2.18.

https://www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018

What if I require further information?

Please contact *Alison Maunder* should you wish to discuss the research further before deciding whether or not to participate via email address: alison.maunder@westernsydney.edu.au or phone 0417800355

What if I have a complaint?

If you have any complaints or reservations about the ethical conduct of this research, you may contact the Ethics Committee through Research Integrity and Ethics on Tel +61 2 4736 0229 or email humanethics@westernsydney.edu.au.

Any issues you raise will be treated in confidence and investigated fully, and you will be informed of the outcome.

This study has been approved by the Western Sydney University Human Research Ethics Committee. The Approval number is H14745 February 2022.