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ARTICLE

Effectiveness of naturopathy for pregnancy in women with diminished ovarian reserve: feasibility randomized controlled trial

BIOGRAPHY

Alison Maunder is a PhD candidate at NICM Health Research Institute, Western Sydney University, Australia and her thesis explores the role of naturopathy for women with diminished ovarian reserve. Her research interests include women's health, infertility and traditional integrative and complementary medicine.

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KEY MESSAGE

Optimal management of women with diminished ovarian reserve (DOR) attempting to conceive is inconclusive. Many women trying to conceive seek naturopathic care. The benefits and risks for improved fertility, however, have not been determined. Evaluation of whole-system naturopathy through a RCT was feasible, acceptable and well-tolerated by women with DOR.

ABSTRACT

Research question: Is conducting a randomized control trial (RCT) to assess the effectiveness of whole-system naturopathy in improving pregnancy rates among women with diminished ovarian reserve (DOR) feasible?

Design: A two-arm, parallel group, assessor-blinded feasibility RCT was conducted. Women with DOR, trying to conceive naturally or by ART, were randomly assigned to naturopathy plus usual care, or usual care alone for 16 weeks. Primary outcomes were feasibility (recruitment, adherence, retention rates), acceptability and safety. Secondary outcomes included ongoing pregnancy rates, live birth rates and health-related outcomes (mental health, quality of life, diet, exercise, sleep and weight). Statistical significance of the differences between the two groups (*P*-values) were exploratory.

Results: One hundred and fifteen women completed the screening survey between March and November 2022. Of these, 66 women were assessed for eligibility and 41 (62%) consented. Recruitment resulted in seven enrolments each month. All 41 participants (100%) adhered to the intervention, 38 (93%) completed end-point questionnaires, 32 (78%) found study participation to be acceptable and 18 out of 21 (86%) from the intervention group would recommend a naturopathic intervention to other women with DOR. The naturopathic treatment was associated with only mild and temporary adverse events. No between-group differences were observed for pregnancy and live birth rates.

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KEYWORDS

Diminished ovarian reserve
Pregnancy
Complementary medicine
Naturopathy
Feasibility

Conclusion: The evaluation of whole-system naturopathy through a RCT was feasible and the treatment was acceptable and well tolerated according to women with DOR. Outcomes from this study will help inform sample size calculations powered for fertility outcomes for future RCTs on this topic.

INTRODUCTION

About 17.5% of the global adult population will experience infertility, with prevalence ranging from 17.8% in high-income countries to 16.5% in low- and middle-income countries (*WHO, 2023*). Infertility is defined by the failure to achieve pregnancy after 12 months or more of regular unprotected sexual intercourse (or 6 months for women aged over 35 years). It negatively affects many aspects of health and personal relationships, and has social and economic consequences through negative population growth (*Boivin et al., 2007*). Diminished ovarian reserve (DOR) is a risk factor for infertility, and is characterized by a reduction in the quantity of oocytes remaining in the ovary (*Cohen et al., 2015*; *Guzel et al., 2017*). Ovarian reserve is influenced by age, genetics and environmental variables (*Greene et al., 2014*; *Ge et al., 2019*). Ovarian reserve naturally declines with age, although the rate of decline varies considerably, and some women experience a decrease beyond what is physiologically expected as a result of normal age-related decline (*Cohen et al., 2015*). About 10% of women seeking medically assisted reproduction (MAR) are diagnosed with DOR (*Scott and Hofmann, 1995*; *Levi et al., 2001*).

The management of women with DOR, who are trying to conceive, currently lacks clear guidelines. The first-line treatment involves MAR, such as ovarian stimulation with gonadotrophins followed by intrauterine insemination and IVF (*ASRM, 2012*; *Artini et al., 2013*; *Buckett and Sierra, 2019*). The success rate of MAR, however, is significantly lower in women with DOR compared with women with normal ovarian reserve (*Meng et al., 2017*), and women with DOR frequently seek other treatments to augment MAR and to maximize fertility.

Many women consult a naturopath to help them conceive, either spontaneously or with MAR treatments (*Steel et al., 2017*; *Women's Health Survey Expert Advisory Group, 2020*). Reasons for seeking naturopathic care include the following: desiring to conceive naturally; to maintain health and wellbeing; to maximize success of MAR treatment; and to explore other options after unsuccessful MAR attempts (*Rayner et al., 2009*; *Rayner et al., 2011*; *Charaf et al., 2015*).

Naturopathy may offer potential benefits alongside usual care; however, the effects are theoretical because currently insufficient evidence is available for the effectiveness of naturopathy on reproductive outcomes. Although evidence that women use naturopathy as a replacement for medical care, including MAR, is lacking, its use may delay accessing further medical options. Potential risks associated with naturopathic care include the lost opportunity of successful MAR caused by time delays, interactions between naturopathic treatments and MAR pharmaceuticals, and the uncertainties surrounding the safety of naturopathic treatments. Therefore, to assess the potential value of naturopathy as a means of improving pregnancy rates, a study was designed to assess the acceptability of a naturopathic intervention and the feasibility of conducting a future large-scale randomized controlled trial (RCT).

Effective feasibility studies can anticipate difficulties with recruitment, adherence, retention, acceptability, delivery of the intervention and safety (*Craig et al., 2013*). Accordingly, the feasibility phase before an RCT helps to maximize the likelihood of researchers evaluating the optimum intervention using the most appropriate and proficient recruitment processes and trial design (*O'Cathain et al., 2015*). Feasibility studies, therefore, play an important role in assessing the potential for conducting a study in the intended environment, shaping an appropriate study design for successful completion and allocating research funds prudently.

The aim of the present study was to establish the feasibility, acceptability and safety and to explore the effectiveness of naturopathy as it is practised in the real world on a range of outcomes important to women with DOR. These data will inform a future adequately powered RCT to evaluate the effectiveness of whole-system naturopathy for improved pregnancy rates in women with DOR.

MATERIALS AND METHODS

Design

A prospective two-armed assessor-blind randomized-controlled feasibility trial, was conducted, with a 16-week intervention period. The study protocol (version 3, 25 November 2021) (Supplementary protocol) was designed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (*Chan et al., 2013*) and Good Clinical Practice guidelines (*Therapeutic Goods Administration, 2016*). This trial was reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 extension for randomized pilot and feasibility trials (*Eldridge et al., 2016*) in conjunction with the Template for Intervention Description and Replication (*Hoffmann et al., 2014*), CONSORT statement reporting randomized, controlled trials of herbal interventions (*Gagnier et al., 2006*), extension of the CONSORT statement for reporting harms (*Ioannidis et al., 2004*). Ethics approval was obtained from the Western Sydney University Human Research Ethics Committee (H14745, February 2022). The trial was prospectively registered on the Australian New Zealand Clinical Trial Registry on 23 December 2021 (ACTRN12621001769875). Recruitment commenced in February 2022 and the study was completed in November 2022.

Participants

Inclusion criteria were women aged between 18 and 40 years, trying to achieve pregnancy, with regular menstrual cycles (every 21–35 days) and a clinical diagnosis of DOR. Diminished ovarian reserve was defined as including one or more of the following markers: elevated basal FSH levels of above 10 IU/l; anti-Müllerian hormone (AMH) lower than 1.1 ng/ml or 7.85 pmol/l; antral follicle count (AFC) fewer than five follicles; and fewer than four oocytes retrieved in a previous IVF stimulated cycle according to the Bologna Criteria (*Ferraretti et al., 2011*). Exclusion criteria were individuals that had been breastfeeding within the previous 6 weeks, severe renal or hepatic disease or abnormal full blood count, urea and electrolytes or liver function tests.

Recruitment, setting and informed consent

Women with DOR in Australia were recruited from medical and traditional, complementary, integrative medicine clinics, women's health organizations and social media. Advertisements directed interested individuals to an online screening survey using Research Electronic Data capture (REDCap) version 8.5.7 (Vanderbilt University, Nashville, USA). A researcher contacted potential participants to provide detailed trial information and to ensure that they understood the participant information sheet. Eligibility was determined through three phases: online screening; confirmation of DOR diagnosis; and normal results in safety blood tests. Eligible participants electronically provided informed consent, completed baseline questionnaires and were randomized.

Randomization, allocation concealment and blinding

Participants were randomized in a 1:1 ratio to the intervention or control group using an internet-based central randomization service (sealedenvelope.com). The randomization sequence, generated by an external researcher, was electronically stored in a restricted-access folder linked to the REDCap project and used for consecutive group allocations. Participants, naturopaths and the primary investigator were not blinded to group allocation owing to the nature of the intervention. Baseline data collection was blinded, but subsequent data collection was unblinded. Analyses were conducted by a blinded investigator.

Interventions

Participants were randomized to naturopathy plus usual care, or usual care alone for 16 weeks. The naturopathic intervention was informed by a Delphi study conducted by the research team (*Maunder et al., 2024a*). The Delphi study defined the practice of naturopathy as a complex intervention, and identified the key components of naturopathic management for women with DOR.

Naturopathy was provided by two accredited naturopaths with Bachelor's degrees in naturopathy and a minimum of 5 years of clinical experience. Training on research methods was provided along with a Practitioner Training Manual. Consultations were provided as telehealth online video meetings, in response to the restrictions of the coronavirus 2019 pandemic (COVID-19).

Participants in the naturopathy group attended four consultations over 16 weeks. An initial 75-min consultation was followed by three 45-min sessions at 4–6-week intervals. Naturopaths conducted case analyses considering health history, current health status, dietary and lifestyle practices, fertility risks and barriers to conception. Follow-up consultations involved reviewing progress, collecting data and adjusting treatments according to clinical indicators and individual needs. Naturopaths provided information on dietary patterns, lifestyle practices, education about ovulation cycles, optimal intercourse timing and self-management strategies that varied according to the clinical presentation of each participant. After each consultation, naturopaths recommended tailored daily supplement regimens (TABLE 1) and herbal medicine formulations (TABLE 2). Participants were advised to discontinue herbal medicine formulas upon conception owing to the absence of safety data in pregnancy (*Mills and Bone, 2005*). Detailed records were kept of the quantity and dosing regimen of each supplement, and all supplements and herbal medicines were dispensed centrally.

The control group received iodine and folate supplements (TABLE 3) per National Health and Medical Research Council recommendations for the pre-pregnancy period (*NHMRC, 2020*). Participants already taking these supplements could choose to continue with their own. At week 8, a 'stay in touch' conversation, without health advice, was conducted by a research assistance to encourage engagement in the trial.

Both groups continued with their usual care from reproductive health and medical teams, including any use of MAR. All medications required for co-morbid conditions were permitted during the trial. Additionally, all participants were informed about publicly available lifestyle advice provided on the 'Your Fertility' website https://www.yourfertility.org.au/, a national public education programme.

Demographics and clinical data

Participant details that were collected at baseline included the following: demographics, reproductive history, medical conditions, use of health practitioners, MAR and traditional, complementary, integrative medicine, lifestyle habits and medications.

Outcomes

Primary outcomes

The primary outcome of the trial was feasibility assessed as follows: recruitment (number completing the screening survey and number of enrolments each month of active recruitment); adherence to the interventions (the number attending the naturopathic consultations and compliance with supplements [in both groups] assessed with a weekly yes/no question and supplement log [dispensed supplements, dosage, and remaining supplements]); retention rate (the number that completed the end-point questionnaires compared with the number that completed the baseline questionnaires; acceptability of the trial to participants was assessed by using an exit questionnaire, designed by the research team, to capture participant's experiences and satisfaction with the trial at end point; safety (the severity and causality of adverse events assessed with a weekly questionnaire; safety blood tests (full blood count, urea and electrolytes and liver function tests) were reviewed and abnormal results reported as adverse events for the intervention group at week 16. All adverse events were recorded, reported and followed up until resolved and assessed for severity and causality.

Before the study, five criteria were set to determine feasibility: recruitment (two or more participants enrolled per month); adherence rate: at least 75% of participants attended at least three of the four naturopathic consultations and at least 75% adhered to the dosing schedule for the 16-week time frame; retention rate (at least 75% of participants completed the end-point questionnaires); acceptability rate (at least 75% of participants reported on the exit questionnaire that they would recommend the naturopathic programme to other women with DOR); and safety (the naturopathic interventions caused only mild and temporary effects).

Secondary outcomes

Pregnancy and live birth rates

The primary outcome for a fully powered trial will be pregnancy and live birth rates

TABLE 1 INTERVENTION GROUP: SUPPLEMENT INGREDIENTS

Full Name	ARTG identifier	Ingredients	Excipients
Eagle Omega Vital Pure Omega-3[a]	204123	Concentrated fish Omega-3 triglycerides 1000 mg equivalent: eicosapentaenoic acid 400 mg equivalent: docosahexaenoic acid 200 mg	Flavour, gelatin, glycerol, mixed (low-alpha type) tocopherols concentrate, purified water and vanillin.
Eagle Tresos Natal[a]	315610	Ascorbic acid 50 mg Biotin 400 μg Borax 2.2 mg equivalent: boron 250 μg Calcium citrate tetrahydrate 236.97 mg equivalent: calcium 50 mg Calcium folinate 347 μg equivalent: folinic acid 250 μg Calcium pantothenate 30 mg equivalent: pantothenic acid 27.48 mg equivalent: calcium 2.52 mg Choline bitartrate 300 mg equivalent: choline 123.39 mg Chromium nicotinate 416 μg equivalent: Chromium 50 μg Colecalciferol 0.025 mg Inositol 40 mg Iron amino acid chelate 37.5 mg equivalent: iron 7.5 mg Levomefolate calcium 270.7 μg equivalent: levomefolic acid 250 μg Magnesium amino acid chelate 100 mg equivalent: magnesium 20 mg Manganese amino acid chelate 20 mg equivalent: manganese 2 mg Mecobalamin (co-methylcobalamin) 500 μg Molybdenum trioxide 75 μg equiv: molybdenum 50 μg Nicotinamide 30 mg Nicotinic acid 5 mg Phytomenadione 0.1 mg Potassium iodide 353.2 μg equivalent: potassium 83.2 μg equivalent: iodine 270 μg Pyridoxal 5-phosphate monohydrate 10 mg equivalent: pyridoxine 6.38 mg Pyridoxine hydrochloride 40 mg equivalent: pyridoxine 32.91 mg Riboflavin 30 mg Selenomethionine 124 μg equivalent: selenium 50 μg Thiamine hydrochloride 30 mg equivalent: thiamine 26.75 mg Zinc amino acid chelate 75 mg equivalent: zinc 15 mg	Acacia calcium hydrogen, phosphate dihydrate, Carnauba Wax, chlorophyllin-copper complex, colloidal anhydrous silica, croscarmellose sodium, crospovidone, d-alpha-tocopherol, fractionated coconut oil, Hypromellose, iron oxide black, liquid glucose, macrogol 8000, magnesium stearate, microcrystalline cellulose, povidone, silicon dioxide, sodium ascorbate, sucrose.
Mediherb Ubiquinol Forte 300[b]	290747	Ubiquinol-10 300 mg	Coconut oil, gelatin, glycerol, iron oxide black, lecithin, purified water, rice bran oil, yellow beeswax.
Mediherb Vitamin D spray[b]	322174	Colecalciferol 1000IU or 25 μg/spray	dl-alpha-tocopherol, flavour, rice bran oil, Stevia rebaudiana, vegetable oil.
Orthoplex zinc citrate[c]	217320	Zinc sulfate heptahydrate 6 mg/ml equivalent: zinc 30 mg	citric acid, potassium sorbate, purified water.

[a] Manufactured by Eagle Professional Natural Medicine, PO Box 4854, Eight Mile Plains, QLD 4113.
[b] Manufactured by MediHerb, PO Box 4854, Eight Mile Plains, QLD 4113.
[c] Manufactured by Bio Concepts, 19A Guardhouse Road, Banyo, QLD 4014.
ARTG, Australian Register of Therapeutic Goods.

because of the importance of these outcomes to women with DOR, as determined by a survey conducted by the research team (*Maunder et al., 2024b*). Pregnancy was assessed throughout the trial until week 16, and participants were contacted at 28 weeks after baseline, based on a recent study of women with low AMH that found most pregnancies occurred within 4–6 months (*Korsholm et al., 2018*). Pregnancies were reported in three phases: clinical pregnancy; ongoing pregnancy; and live birth. Clinical pregnancy was assessed as evidence of a gestational sac with fetal heart motion at 6 weeks and over on ultrasound. Ongoing pregnancy rate was assessed as a viable pregnancy at 20 weeks. Miscarriages were also reported.

Menstrual cycle characteristics

For the duration of the trial, participants self-recorded menstrual cycle characteristics, including the following: the

TABLE 2 INTERVENTION GROUP: HERBAL MEDICINES

Botanical name	Common name	TGA identifier	Plant part (dried)	Concentration mg:ml	Ethanol content, %	Recommended dose per week, ml	Standardized active ingredient (if applicable)
Asparagus racemosus[a]	Shatavari	104660	Root	1:2	45	30–60	
Angelica polymorpha[a]	Dong quai	72121	Root	1:2	45	30–60	
Actaea racemosa[a]	Black cohosh	108175	Root	1:2	60	10–30	Minimum of 15 mg/ml triterpene glycosides as 27-deoxyactein.
Cinnamomum spp[a]	Cinnamon	67430	Bark	1:4	70	30–60	
Curcuma longa	Turmeric	65400	Rhizome	1:1	69	35–100	Not less than 2 mg/ml of curcuminoids.
Dioscorea villosa[a]	Wild yam	62623	Root and rhizome	1:2	60	20–40	Not less than 15 mg/ml steroidal saponins.
Ginkgo biloba[a]	Ginkgo	67157	Leaf	2:1	50	21–28	9.6 mg/ml ginkgo flavone glycosides.
Glycyrrhiza glabra[a]	Licorice	62323	Root	1:1	20	15–40	Not less than 30 mg/ml of glycyrrhizin.
Paeonia lactiflora[a]	Peony	68507	Root	1:2	45	30–60	
Rehmannia glutinosa[a]	Rehmannia	94996	Root	1:2	23	30-60	
Matricaria chamomilla[a]	Chamomile	108207	Flower	1:2	60	20–40	Not less than 0.3 mg/ml of alpha-bisabolol.
Tribulus terrestris[a]	Tribulus	83708	Aerial parts	2:1	60	50–100	Not less than 30 mg/ml or furostanol saponins as protodioscin.
Vitex agnus-castus[a]	Chaste tree	70352	Fruit	1:2	60	6–30	
Withania somnifera[a]	Withania	84964	Root	2:1	45	10–30	Not less than 4.0 mg/ml of withanolides.
Zingiber officinale[a]	Ginger	62337	Rhizome	1:2	90	5–15	

[a] Manufactured by MediHerb, PO Box 4854, Eight Mile Plains, QLD 4113.

All herbal medicines are listed with the Therapeutics Goods Administration (TGA) in the Australian Approved Names for Therapeutic Substances List.

TABLE 3 CONTROL GROUP: SUPPLEMENT INGREDIENTS

Full Name	ARTG number	Ingredients	Excipients
Orthoplex Iodine[a]	314850	Potassium iodide 294 μg equivalent iodine 225 μg	Colloidal anhydrous silica, disodium edetate, gellan gum, glycine, hypromellose, leucine, potable water, potassium acetate.
Orthoplex Folinic acid[a]	275078	Calcium folinate 540 μg equivalent folinic acid 500 μg	Colloidal anhydrous silica, disodium edetate, gellan gum, glycine, hypromellose, leucine, potable water, potassium acetate.

[a] Manufactured by Bio Concepts, 19A Guardhouse Road, Banyo, QLD 4014.

ARTG, Australian Register of Therapeutic Goods.

first day of the menstrual period; duration of their menstrual cycles; and signs and symptoms that were experienced.

Anthropometric measurements

Anthropometric measurements including self-reported weight, height and waist circumference, were collected at baseline and week 16.

Psychological outcomes

Psychological outcomes were measured at baseline and week 16 using the Depression, Anxiety and Stress Scale (DASS-21), a validated instrument of three scales for depression, anxiety and stress (seven items each) with scores ranging from 0 to 21. Higher scores indicate more distress (*Henry and Crawford, 2005*).

Health-related quality of life

Health-related quality of life was measured at baseline and week 16 using the Fertility Quality of Life questionnaire (FertiQoL), a fertility-specific validated questionnaire, comprising a core module (24 items) and a treatment module (10 items). The core module covers emotional, mind–body, relational and social domains, whereas the treatment module addresses environmental and tolerability aspects. Scores range from 1 to 100, with higher scores indicating better quality of life (*Kitchen et al., 2017*).

Lifestyle factors

Lifestyle characteristics, including dietary intake, physical activity and sleep patterns, were measured at baseline and week 16 using validated tools: Dietary Guideline Index (DGI), International Physical Activity Questionnaire (IPAQ), and Pittsburgh Sleep Quality Index (PSQI). The DGI (24 items) assesses diet quality according to Australian Dietary Guidelines giving scores ranging from 0–100 with higher scores indicating a healthier diet (*McNaughton et al., 2008*; *Thorpe et al., 2016*). The IPAQ

(seven items) calculates metabolic equivalent of tasks (MET) minutes per week; one MET is the energy expended when at rest. Higher MET scores indicate greater physical activity (*Craig et al., 2003*). The PSQI (nine items) assess sleep quality with scores from 0–21; higher scores indicate worse sleep quality based on seven subscales (*Buysse et al., 1989*).

Credibility outcomes

Credibility and expectancy in the naturopathy group were assessed using the Credibility/Expectancy Questionnaire (CEQ) comprising thoughts (four items) and feelings (two items). Credibility was derived from the first three thought items, whereas expectancy came from the fourth thought question and the two feeling questions (*Devilly and Borkovec, 2000*). The maximum score on each subscale is 27, with higher scores indicating positive beliefs about naturopathy. A score of 13.5 is considered neutral, scores above are positive, whereas scores below are negative (*Devilly and Borkovec, 2000*). The CEQ was administered immediately after the first naturopathic consultation.

Data collection

Data were collected by participants completing online questionnaires into REDCap software (*Harris et al., 2009*).

Sample size

A power calculation was not conducted as this was a feasibility study. The primary objective was to assess feasibility of RCT methodology evaluating naturopathy for improved pregnancy rates in women with DOR and establish data for power calculations in subsequent RCTs. A sample size of 40 participants (20 per group), with a possible dropout rate of 20% (based on previous studies in this population (*Xu et al., 2018*), allowed us to observe practicalities of recruitment, acceptability of naturopathy, retention and to detect any adverse events at a rate of 10% or greater (*Viechtbauer et al., 2015*).

Statistical analysis

Analyses were conducted by a blinded investigator using R Studio (version 4.1.1) (*R Core Team, 2021*). Recruitment, retention and adherence rates were described as percentages and proportions for categorical variables and as means and SD for continuous variables. Participant characteristics were described at baseline. Patient age, AMH level, body weight, body mass index, waist circumference and days between menstrual cycles were reported as medians with an interquartile range owing to skewed distribution of the small sample size. Adverse events were described and categorized as both the number of participants with any event and the total number of events.

Because of the feasibility study design, this trial was not powered to detect differences in any secondary outcomes. Therefore, all *P*-values for secondary outcomes should be considered exploratory not confirmatory. Between-group continuous outcomes were calculated using the Wilcoxon rank sum test or Welch two sample t-test, determined by non-normal or normal distribution of data for each variable. Between-group differences were analysed using analysis of covariance, adjusting for baseline scores as a co-variate and reported with 95% confidence intervals.

Analyses were conducted on an intention-to-treat basis, and data from participants who withdrew were analysed according to their group of random assignment. Missing end-point data were imputed with the last observation carried forward method.

Results

One hundred and fifteen women completed the screening survey for the RCT between March and November 2022. A total of 66 women were assessed for eligibility and, of those, 41 consented to participate in the trial and completed the baseline questionnaires (FIGURE 1).

Baseline data

The demographic, medical and reproductive characteristics of participants are presented in TABLE 4. The mean age of the women and their male partners was 36.2 ± 3.1 and 38.1 ± 5.3 years, respectively. Most women had been diagnosed with DOR in the past 2 years, were currently undergoing, or had previously used, MAR and did not have any biological children. To enhance fertility, women had primarily sought assistance from general practitioners, fertility specialists, acupuncturists, and used meditation and massage practices. Endometriosis was the most common medical condition, with six women in each group being affected. Two participants (9.5%) in the intervention group and one (5.0%) in the control group, who were undergoing MAR reported a severe effect on their male partner's fertility.

Recruitment, retention and adherence

Recruitment resulted in an average of 20 enquiries and seven enrolments each month of active recruitment and met our criteria for success for recruitment rate. The conversion rate from completing the screen survey to enrolment was 35.7% (41/115), and from those assessed for eligibility to enrolment was 62.1% (41/66). Of those that were excluded, 46% (34/74) did not respond to contact, 23% (17/74) did not meet the study's inclusion criteria, 19% (14/74) did not provide consent or complete the safety blood tests and 12% (9/74) declined to participate (FIGURE 1).

End-point questionnaires were completed by 93% (38/41) of participants, and both groups met our criteria for success for retention rate. Of the women who enrolled, four (10%) withdrew or were lost to follow-up from baseline to end point (week 16). From the control group, one woman withdrew from the trial after randomization on advice from a fertility specialist, and two women were lost to follow-up. From the intervention group, one woman withdrew at week 15 after a new medical condition was diagnosed; however, she agreed to complete the end-point questionnaires.

Adherence with the naturopathic intervention was high with all women attending at least three naturopathic consultations in the intervention group and meeting our criteria for success. Compliance with nutritional supplements and herbal medicines was high, with 97.2% of participants reporting in their weekly questionnaires that they were taking the supplements. At the end of the study, 76% and 74% of participants in the intervention group and control groups respectively, counted and reported any excess supplements and herbal medicines. On the basis of this information, compliance in the intervention group exceeded the a-priori criterion of 75% for the prenatal multivitamin, herbal medicine, ubiquinol and zinc supplements. Compliance with vitamin D and fish oil supplements was lower at 70% and 60%, respectively. In the control group, compliance with folic acid and iodine supplements was 95% and 92%, respectively and met our criteria for success. The most common reason for supplement non-compliance was being on vacation (4/40 [10%]), based on the weekly questionnaire data (Supplementary Table 1).

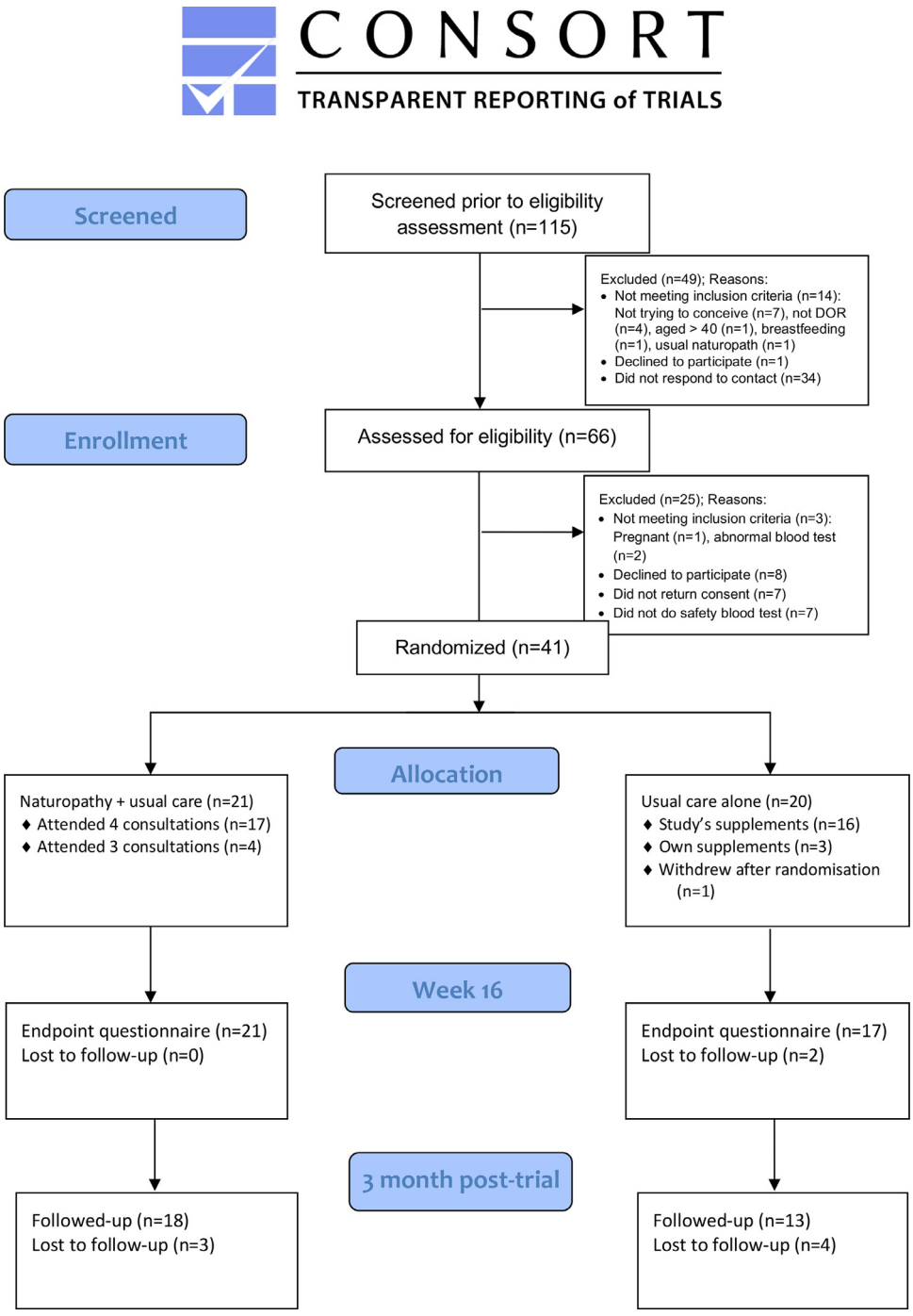

FIGURE 1 Enrolment and analysis (CONSORT diagram). DOR, diminished ovarian reserve (*Eldridge* et al., *2016*).

Acceptability: exit questionnaire data

Acceptability of the naturopathic intervention was high and met our criteria for success, with most participants from the intervention group (18/21 [86%]) 'definitely' willing to recommend a naturopathic intervention to other women with DOR (TABLE 5). Being satisfied with their trial experience was 'strongly agreed' or 'agreed' by 95% (20/21) and 70% (12/17) of women in the intervention and control groups, respectively. Women in the intervention group (18/21) found that the extra attention on health and wellbeing was beneficial. This differed significantly to the women in the control group (4/17) ($P < 0.001$).

When participants were asked about their dislikes, 10 in the intervention group and eight in the control group found 'nothing' negative in the trial. The next most common answers were that they did not like having the safety blood tests (9/38) and they spent more time thinking about pregnancy (6/38).

Safety

Naturopathic treatment was considered to be low risk, causing only mild and temporary adverse events, and met our criteria for safety. No between-group differences were found for adverse events

TABLE 4 BASELINE DEMOGRAPHIC, MEDICAL AND REPRODUCTIVE CHARACTERISTICS

Characteristic		Intervention + usual care (*n* = 21)	Usual care alone (*n* = 20)
		Median (IQR)/ *n* (%)	Median (IQR)/ *n* (%)
Age, years		36.0 (34.0–39.0)	38.5 (34.8–39.0)
State of residence	New South Wales	10 (47.6)	12 (60.0)
	Victoria	6 (28.6)	4 (20.0)
	Queensland	2 (9.5)	2 (10.0)
	Western Australia	2 (9.5)	2 (10.0)
	South Australia	1 (4.8)	0 (0.0)
Year diagnosed with DOR	2022 (<12 months)	4 (19.0)	4 (20.0)
	2021 (1–2 years)	8 (38.1)	8 (40.0)
	2020 (2–3 years)	3 (14.3)	3 (15.0)
	2019 (3–4 years)	2 (9.5)	1 (5.0)
	2018 (4–5 years)	1 (4.8)	1 (5.0)
	5 years or more	3 (14.3)	3 (15.0)
Anti-Müllerian hormone, pmol/l		4.3 (2.8–6.8)	5.0 (2.6–6.7)
Weight, kg		74.0 (64.0–85.0)	73.0 (62.2–86.8)
BMI calculated, kg/m^2		27.1 (23.4–31.8)	26.2 (23.2–31.9)
	<24.9	8 (38.1)	6 (30.0)
	25.0–29.9	6 (28.6)	5 (25.0)
	≥30.0	7 (33.3)	9 (45.0)
Waist circum-ference, cm		91.0 (76.0–97.0)	84.0 (75.5–95.3)
Menstrual cycle	Number with regular cycles	19 (90.5)	18 (90.0)
	Number of days per cycle	26.0 (26.0–29.5)	28.0 (27.0–28.8)
	Number with irregular cycles	2 (9.5)	2 (10.0)
Ethnicity	European, Anglo Saxon, Caucasian	18 (85.7)	13 (65.0)
	Mixed ethnicity	2 (9.5)	3 (15.0)
	Asian	0 (0.0)	2 (10.0)
	North African, Middle eastern	1 (4.8)	1 (5.0)
	Oceanic	0 (0.0)	1 (5.0)
Education	Higher school certificate	3 (14.3)	0 (0.0)
	TAFE or vocational certificate	2 (9.5)	5 (25.0)
	Bachelor's degree	9 (42.9)	9 (45.0)
	Post-graduate degree	7 (33.3)	6 (30.0)
Employment	Full-time	16 (76.2)	11 (55.0)
	Part-time or casual	2 (9.5)	6 (30.0)
	Self-employed	1 (4.8)	2 (10.0)
	Home duties or caring for children, family, or both	1 (4.8)	1 (5.0)
	Unable to work	1 (4.8)	0.(0.0)
Had previously seen a naturopath	No	12 (57.1)	12 (60.0)
	Yes, in the past 12 months	4 (19.0)	2 (10.0)
	Yes, more than 1 year ago	5 (23.8)	6 (30.0)
Number of cigarette smokers	Never smoked	16 (76.2)	14 (70.0)
	Smoked in the past	5 (23.8)	4 (20.0)
	Current smoker	0 (0.0)	2 (10.0)
Number using recreational drugs	Never used	15 (71.4)	12 (60.0)
	Used in the past	6 (28.6)	8 (40.0)

(*continued on next page*)

TABLE 4 (*Continued*)

Characteristic		Intervention + usual care (*n* = 21)	Usual care alone (*n* = 20)
		Median (IQR)/ *n* (%)	Median (IQR)/ *n* (%)
Health providers seen in the past 12 months to assist with fertility	General practitioner	17 (81.0)	16 (80.0)
	Fertility specialist	15 (71.4)	17 (85.0)
	Gynaecologist	8 (38.1)	8 (40.0)
	Fertility nurse	7 (33.3)	5 (25.0)
	Psychologist	3 (14.3)	3 (15.0)
	Obstetrician	3 (14.3)	2 (10.0)
	Fertility counsellor	3 (14.3)	1 (5.0)
	Physiotherapist or exercise physiologist	2 (9.5)	1 (5.0)
	Dietician	1 (4.8)	1 (5.0)
	Reproductive immunologist	0 (0.0)	1 (5.0)
TCIM providers seen in past 12 months to assist with fertility	Acupuncturist	10 (47.6)	10 (50.0)
	Naturopath	3 (14.3)	3 (15.0)
	Chinese medicine practitioner	2 (9.5)	4 (20.0)
	Chiropractor or osteopath	1 (4.8)	2 (10.0)
	Nutritionist	1 (4.8)	1 (5.0)
	Kinesiologist	0 (0.0)	1 (5.0)
	Reiki practitioner	1 (4.8)	0 (0.0)
Self-help practices used in the past 12 months to assist with fertility (%)	Meditation	7 (33.3)	8 (40.0)
	Massage	1 (4.8)	9 (45.0)
	Yoga	4 (19.0)	5 (25.0)
	Relaxations techniques	2 (9.5)	5 (25.0)
	Prayer	1 (4.8)	5 (25.0)
	Visualization	1 (4.8)	4 (20.0)
	Reflexology	0 (0.0)	1 (5.0)
Concomitant medical conditions	Endometriosis	6 (28.6)	6 (30.0)
	MTHFR polymorphisms	4 (19.0)	2 (10.0)
	Polycystic ovary syndrome	0 (0.0)	2 (10.0)
	Under-active thyroid	0 (0.0)	2 (10.0)
	Over-active thyroid	1 (4.8)	1 (5.0)
	Rheumatoid arthritis	1 (4.8)	0 (0.0)
	Cancer	0 (0.0)	1 (5.0)
	Uterine polyps	1 (4.8)	0 (0.0)
	Elevated blood pressure	0 (0.0)	1 (5.0)
	None of these medical conditions	9 (42.9)	10 (50.0)
Number MAR	Previous treatment	7 (33.3)	6 (30.0)
	Current treatment	5 (23.8)	5 (25.0)
	Considering treatment in the future	5 (23.8)	5 (25.0)
	Not using or have not used MAR	4 (19.0)	4 (20.0)
Types of MAR used	Ovulation tracking	5 (23.8)	3 (15.0)
	Natural cycle artificial or IUI	3 (14.3)	1 (5.0)
	Ovulation induction with oral medication	6 (28.6)	3 (15.0)
	Ovulation induction with injectable fertility drugs	7 (33.3)	4 (20.0)
	Ovulation induction with gonadotrophins and IUI	3 (14.3)	1 (5.0)

(*continued on next page*)

TABLE 4 (*Continued*)

Characteristic		Intervention + usual care (*n* = 21)	Usual care alone (*n* = 20)
		Median (IQR)/ *n* (%)	Median (IQR)/ *n* (%)
	Ovulation induction with gonadotrophins and IVF	3 (14.3)	8 (40.0)
	IVF and ICSI	5 (23.8)	5 (25.0)
	Frozen embryo transfer in natural cycle	2 (9.5)	5 (25.0)
	Frozen embryo with ovulation induction	0 (0.0)	3 (15.0)
	Fertility preservation	1 (4.8)	2 (10.0)
MAR cycles	Number	2 (0.0–5.0)	1 (0.0–4.2)
	Range	1–14	1–12
Number of biological children	No children	19 (90.5)	11 (55.0)
	1	2 (9.5)	7 (35.0)
	2	1 (4.8)	2 (10.0)
Type of conception (*n* = 12)	Conceived naturally	2 (66.7)	7 (77.8)
	Conceived with MAR	1 (33.3)	2 (22.2)
Male partner's age		39.5 (35.5–41.0) (*n* = 20)	39.0 (33.8–40.2) (*n* = 20)
Status of male partner's fertility	No effect of male fertility	14 (70.0)	12 (60.0)
	Mild to moderate effect	3 (15.0)	2 (10.0)
	Severe effect on male fertility	2 (10.0)	1 (5.0)
	Not known, no tests have been done	1 (5.0)	5 (25.0)

BMI, body mass index, DOR, diminished ovarian reserve; ICSI, intracytoplasmic sperm injection,IUI, intrauterine insemination; IQR, interquartile range, IUI, intrauterine insemination, MAR, medically assisted reproduction; MTHFR, methyltetrahydrofolate reductase; TAFE, Technical and Further Education; TCIM, traditional, complementary and integrative medicines.

(*P* = 0.65) (Supplementary Table 2) and no participants withdrew because of adverse events. One participant reported stomach pains, which were probably related to the intervention; however, severity was minor, resolved in 1 day and no action was required. Of the adverse events possibly related to the intervention (*n* = 8), three reported minor gastrointestinal symptoms (*n* = 3) and one case each of respiratory illness, headaches, anxiety, heart palpitations and menstrual cycle changes. In three cases, participants were advised to stop their herbal medicines until symptoms resolved and then restart at half dose. All participants were able to continue with the herbal medicines without further adverse events. One serious adverse event occurred in the control group involving hospitalization of a participant experiencing a miscarriage; however, participation in the trial was not considered to be a cause. No adverse events were reported relating to abnormal safety blood results, from 19 (90.5%) participants in the intervention group that completed the tests.

Secondary outcomes

Clinical pregnancy and ongoing pregnancy (20 weeks or more) at week 28 and total live births are presented in TABLE 6.

The between-group differences at end point for anthropometrics, menstrual cycle length, psychological distress, quality of life, diet quality, level of physical activity and sleep quality are presented in TABLE 7. A lower depression score was shown for women in the intervention group compared with the control group (*P* = 0.032). No other statistically significant differences were observed between groups for any other outcomes.

Experience of naturopathy: exit questionnaire data

The total scores for credibility and expectancy were positive for both measures, as rated by participants in the naturopathic group (FIGURE 2). The women's experiences of the naturopathy consultations are presented in TABLE 8. Most women enjoyed the relationship with the naturopath, liked the approach to health and wellbeing, and found the naturopath's advice to be helpful. When participants were asked what they did not enjoy about the naturopathic intervention, 57% (12/21) of women reported there was 'nothing' that they did not enjoy. The next most common answers were that they did not like taking the herbal medicines (8/21) and they did not like taking the supplements (3/21). When reporting the most important features of the intervention, most women reported their naturopath to be a good listener, empathetic or understanding (14/21 [67%,]) as well as knowledgeable (12/21 [57%]). The qualitative responses of the participants about the most important features of their naturopathic sessions are presented in Supplementary Table 3.

As part of the naturopathic intervention, nutritional supplements and herbal medicines were supplied by the industry partners of the trial and prescribed by the naturopath based on their interpretation of the individual participant. The ingestible substances that were prescribed to participants during the trial is presented in TABLE 9.

TABLE 5 PARTICIPANT SATISFACTION AND EXIT QUESTIONNAIRE

Description	Total) (*n* = 38), *n* (%)	Intervention (*n* = 21), *n* (%)	Control (*n* = 17), *n* (%)	*P*-value[a]
Enjoy/benefits of trial[b]				
Being able to help others with DOR	29 (76.3)	16 (76.2)	13 (76.5)	>0.99
The extra attention to health and wellbeing	22 (58.0)	18 (85.7)	4 (23.5)	<0.001[c]
I became pregnant	7 (18.4)	3 (14.3)	4 (23.5)	0.68
I didn't enjoy being in the trial	3 (8.0)	0 (0.0)	3 (17.6)	0.08
Not enjoy/detrimental about being in the trial[b]				
Nothing I did not enjoy	18 (47.4)	10 (47.6)	8 (47.1)	0.97
Having blood tests	9 (23.7)	4 (19.0)	5 (29.4)	0.70
More time thinking about being pregnant	6 (15.8)	4 (19.0)	2 (11.8)	0.67
Being in the control group	3 (8.0)	0 (0.0)	3 (17.6)	0.08
Recording the menstrual cycle	2 (5.3)	1 (4.8)	1 (5.9)	> 0.99
Testing for pregnancy so frequently	2 (5.3)	2 (9.5)	0 (0.0)	0.49
Surveys were too long	1 (2.6)	0 (0.0)	1 (5.9)	0.45
Recommend similar future trial to friends/family with DOR				
Definitely participate/recommend	26 (68.4)	18 (85.7)	8 (47.1)	0.01[c]
Probably participate/recommend	7 (18.4)	3 (14.3)	4 (23.5)	
I don't know	5 (13.2)	0 (0.0)	5 (29.4)	
No, I would not participate/recommend	0 (0.0)	0 (0.0)	0 (0.0)	
The overall commitment expected in trial				
Much less	6 (15.8)	2 (9.5)	4 (23.5)	0.72
Somewhat less	0 (0.0)	0 (0.0)	0 (0.0)	
Same as expected	25 (65.8)	15 (71.4)	10 (58.8)	
Somewhat more	5 (13.2)	3 (14.3)	2 (11.8)	
Much more	2 (5.3)	1 (4.8)	1 (5.9)	
Satisfied with trial experience				
Strongly agree	19 (50.0)	13 (61.9)	6 (35.3)	0.23
Agree	13 (34.2)	7 (33.3)	6 (35.3)	
Neither agree nor disagree	4 (10.5)	1 (4.8)	3 (17.6)	
Disagree	1 (2.6)	0 (0.0)	1 (5.9)	
Strongly disagree	1 (2.6)	0 (0.0)	1 (5.9)	

[a] Fisher's exact test; Pearson's chi-squared test.
[b] More than one response.
[c] $P < 0.05$.
DOR, diminished ovarian reserve.

TABLE 6 PREGNANCY OUTCOMES AT WEEK 28 (3-MONTH FOLLOW-UP) AND LIVE BIRTHS

Pregnancy outcomes	Intervention (*n* = 21), *n* (%)	Control (*n* = 20), *n* (%)
Clinical pregnancies[a]	4 (19.0)	5 (25.0)
Miscarriages[b]	0 (0.0)	2 (40.0)
Ongoing pregnancies[a]	4 (19.0)	3 (15.0)
Live births[b]	4 (100.0)	3 (60.0)
Type of conception		
Conceived naturally[b]	3 (75.0)	4 (80.0)
Conceived with MAR[b]	1 (25.0)	1 (20.0)

[a] Denominator is all participants.
[b] Denominator is all clinical pregnancies,
MAR, medically assisted reproduction.

TABLE 7 ANTHROPOMETRICS, MENSTRUAL CYCLE, PSYCHOLOGICAL DISTRESS, QUALITY OF LIFE, DIET, PHYSICAL ACTIVITY, SLEEP: BETWEEN-GROUP DIFFERENCES AT 16 WEEKS

Characteristics	Intervention (*n* = 21)		Control (*n* = 20)		Difference between groups at 16 weeks	
	Baseline Mean (SD)	Week 16 Mean (SD)	Baseline Mean (SD)	Week 16 Mean (SD)	Adjusted difference[a]	95% CI[a]
Anthropometrics						
Weight, kg	78.0 (17.0)	79.0 (17.0)	77.0 (18.0)	77.0 (17.0)	1.0	−1.4 to 3.3
BMI, kg/m^2	28.1 (5.7)	28.6 (5.8)	28.2 (6.1)	28.4 (5.7)	0.36	−0.48 to 1.2
Waist circumference, cm	89.0 (15.0)	90.0 (15.0)	85 (20.0)	84.0 (18.0)	3.0	−1.0 to 7.0
Menstrual cycle						
Length, days	26.0 (25.0–29.0)[b]	26.0 (25.0–30.0)[b]	27.5 (25.0– 30.5)[b]	27.0 (25.8– 29.0)[b]	−0.15	−3.1 to 2.8
Psychological wellbeing						
Depression score	4.3 (4.1)	2.2 (2.7)	3.4 (3.5)	3.2 (3.3)	−1.3	−2.6 to −0.13
Anxiety score	2.3 (2.6)	2.2 (2.5)	1.7 (1.9)	2.1 (1.8)	−0.43	−1.4 to 0.51
Stress score	5.9 (3.8)	5.4 (3.5)	5.8 (3.4)	5.2 (4.1)	0.37	−1.4 to 2.2
Quality of life						
Total FertiQoL	58.0 (17.2)	55.0 (15.8)	50.7 (14.8)	51.7 (12.9)	−2.2	−11.0 to 6.8
Core FertiQoL score	61.2 (15.9)	60.2 (19.8)	58.5 (13.2)	58.1 (16.9)	−4.5	−16.0 to 7.5
Emotional subscale	50.2 (20.5)	50.2 (24.7)	46.7 (20.7)	46.9 (23.6)	−3.5	−19.0 to 12.0
Mind–body subscale	56.4 (19.9)	59.6 (23.2)	59.0 (19.4)	57.4 (21.2)	−3.5	−20.0 to 13.0
Relational subscale	79.4 (15.9)	71.9 (20.9)	71.2 (17.3)	71.2 (18.2)	−5.9	−19.0 to 6.8
Social subscale	59.9 (20.9)	58.7 (12.1)	57.1 (20.0)	56.9 (19.4)	−5.1	−15.0 to 5.2
Treatment score	54.2 (21.4)	55.1 (14.5)	55.5 (11.0)	49.2 (14.4)	3.1	−5.6 to 12.0
Environment subscale	55.1 (24.9)	56.1 (19.1)	57.8 (11.6)	52.5 (18.1)	1.8	−8.4 to 12.0
Tolerability subscale	52.8 (23.3)	53.7 (19.4)	52.1 (22.9)	44.2 (15.6)	5.2	−9.5 to 20.0
Diet quality						
Total diet score	61.5 (9.3)	63.0 (9.3)	64.0 (8.5)	66.0 (7.0)	−0.53	−6.8 to 5.8
Fruit consumption	5.2 (5.7)	5.7 (3.0)	6.3 (2.2)	6.7 (2.4)	−0.56	−2.6 to 1.5
Vegetable consumption	8.3 (1.8)	9.0 (1.5)	8.7 (1.8)	9.0 (1.5)	−0.19	−1.3 to 0.91
Grain consumption	4.5 (2.3)	3.8 (2.0)	4.5 (3.0)	5.0 (3.0)	−0.88	−2.6 to 0.80
Protein serves	9.5 (0.9)	9.4 (0.9)	8.5 (2.0)	8.6 (1.8)	0.72	−0.17 to 1.6
Dairy consumption	6.8 (2.0)	5.9 (2.3)	5.7 (2.5)	6.0 (2.3)	−0.59	−2.6 to 1.4
Water consumption	6.8 (1.9)	6.8 (2.0)	6.4 (2.3)	6.6 (2.1)	0.29	−1.1 to 1.7
Discretionary foods	9.9 (5.5)	8.0 (4.0)	6.2 (3.5)	6.1 (3.5)	−0.15	−3.2 to 2.9
Healthy fat	5.2 (1.7)	5.0 (1.7)	5.6 (1.4)	5.4 (1.4)	−0.44	−1.8 to 0.92
Variety of foods	5.5 (0.9)	5.5 (0.9)	5.8 (1.5)	5.7 (1.3)	0.08	−0.82 to 1.0
Physical activity						
Total MET min/week	1820 (1757)	1733 (1007)	1948 (1601)	2014 (1611)	−102	−763 to 559
Vigorous activity MET	310 (496)	419 (479)	542 (839)	388 (742)	104	−255 to 464
Moderate activity MET	600 (1117)	496 (391)	437 (455)	483 (790)	67	−297 to 431
Walking MET	910 (952)	818 (598)	969 (1025)	1143 (1166)	−273	−772 to 225
Time spent sitting on weekdays	371 (167)	397 (212)	378 (152)	372 (158)	38	−65 to 141
Sleep quality						
Total sleep score	6.2 (3.4)	5.4 (2.8)	6.3 (3.7)	6.7 (3.7)	−1.2	−2.9 to 0.44
Sleep duration	1.43 (1.03)	0.81 (0.81)	1.35 (0.99)	1.30 (1.03)	−0.46	−0.94 to 0.03
Sleep latency	0.52 (0.51)	0.38 (0.50)	0.55 (0.76)	0.60 (0.75)	−0.23	−0.52 to 0.05

(*continued on next page*)

TABLE 7 (*Continued*)

Characteristics	Intervention (*n* = 21)		Control (*n* = 20)		Difference between groups at 16 weeks	
	Baseline Mean (SD)	Week 16 Mean (SD)	Baseline Mean (SD)	Week 16 Mean (SD)	Adjusted difference[a]	95% CI[a]
Sleep disturbance	0.43 (0.60)	0.19 (0.40)	0.60 (0.82)	0.55 (0.76)	−0.29-	−0.61 to 0.04
Sleep efficiency	1.14 (0.48)	1.14 (0.36)	1.25 (0.55)	1.35 (0.59)	−0.09	−0.32 to 0.14
Day dysfunction	1.05 (0.86)	0.86 (0.65)	0.80 (0.83)	1.10 (0.85)	−0.25	−0.72 to 0.22
Sleep medications	0.67 (1.15)	1.05 (1.36)	0.65 (1.23)	0.70 (1.22)	0.24	−0.53 to 1.0
Sleep quality	1.00 (0.71)	1.00 (0.63)	1.05 (0.69)	1.10 (0.72)	−10.13	−0.49 to 0.23

[a] Analysis of covariance.

[b] Median (interquartile range).

BMI, body mass index, FertiQoL, Fertility Quality of Life questionnaire; MET, metabolic equivalent of tasks (energy expended at rest).

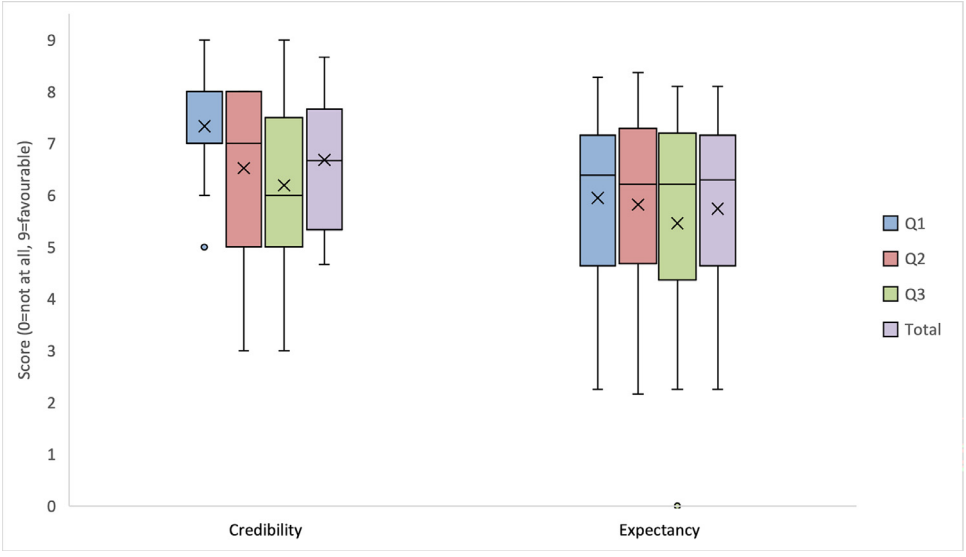

FIGURE 2 Credibility and expectancy questionnaire scores after the initial naturopathy consultation about the naturopathic treatment offered (*n* = 21). Credibility: Question 1 (Q1), how logical does the treatment offered seem to you? Question 2 (Q2), how useful do you think treatment will be for you to achieve pregnancy? Question 3 (Q3), how confident would you be in recommending this treatment to a friend who experiences diminished ovarian reserve? Expectancy: Q1, by the end of the treatment period, how much improvement do you think will occur? Q2, how much do you really feel that treatment will help you to achieve pregnancy? Q3, by the end of the treatment period, what chance of pregnancy do you really feel will occur? Box and whisker plots for credibility and expectancy ratings for naturopathic treatment for improved pregnancy rates. Crosses at the centre of boxes show means and cross bars within boxes show medians. Hinges appear at the 25th and 75th percentile of each distribution. Lower circles reveal outliers that were dropped for analyses. The ends of each whisker show maximum and minimum scores when outliers are removed.

DISCUSSION

This feasibility study demonstrates that a fully powered RCT comparing naturopathy plus usual care against usual care alone for improved pregnancy rates in women with DOR is feasible. The results provide a number of insights pertinent to the success of an adequately powered RCT evaluating pregnancy rates according to the protocol deployed in this feasibility study.

Successful recruitment of women with DOR from a sizeable population provided an adequate sample of consenting participants. The recruitment rate of seven participants per week exceeded our predetermined criterion. Notably, social media advertising was the most successful strategy, contributing to 85% of completed screening surveys and should be considered for future studies. Interestingly, 30% (34/115) of respondents to advertisements completed the initial screening, however, did not respond to follow-up communications, making it unclear if they met the trial's eligibility criteria. The study primarily attracted interest from well-educated, employed and childless white women of European descent, living in capital cities across Australia. The recruitment results reflected the demographic distribution of women aged 20–44 years (*ABS, 2021*), with 78% of participants residing in capital cities.

We assessed adherence as attendance at naturopathic consultations and compliance with the supplement regimen during the 16-week trial. The naturopathic consultations were well attended, possibly owing to reminders and rescheduling of appointments by naturopaths. Despite a large geographic dispersion, the supplement delivery time variations (1–4 days) did not affect compliance. Returning supplement containers, however, became

TABLE 8 PARTICIPANTS' EXPERIENCE OF THE NATUROPATHIC CONSULTATIONS

Questions	Intervention (*n* = 21), *n* (%)
Benefits of naturopathic consultations	
The advice my naturopath gave was helpful	19 (90.5)
I enjoyed the relationship with the naturopath	17 (80.9)
An alternative way of looking at health and wellbeing	16 (76.2)
Improved my approach to fertility	12 (57.1)
Improved my diet	10 (47.6)
Improved my mood	7 (33.3))
Improved my ability to cope with stress	5 (23.8)
Improved my sleep	4 (19.1)
Improved my motivation to exercise	3 (14.3)
Gave me hope that I was taking action to improve fertility	1 (4.8)
I didn't enjoy the consultations	0 (0.0)
Parts of the consultations that I did not enjoy	
There was nothing I did not enjoy	12 (57.1)
I did not like taking the herbal medicines	8 (38.1)
I did not like taking the supplements	3 (14.3)
I did not like the telehealth appointments	1 (4.8)
The follow-up appointments were too short	1 (4.8)
The study was not long enough	1 (4.8)
What were the three most important features of the sessions with your naturopath? (please note if there was nothing important)	
The naturopath:	
Listened, showed empathy, was understanding / supportive	14 (66.7)
Was knowledgeable	12 (51.7)
Offered good advice	9 (42.9)
Provided care for whole-person health	8 (38.1)
I enjoyed the relationship	8 (38.1)
Provided a new approach to fertility	6 (28.6)
I felt better	2 (9.5)
Encouraged introspection	1 (4.8)

impractical owing to the volume and fragility of the containers, leading to a modification being made in the trial; participants were requested to send photographs of the containers instead. Ensuring reliable delivery and an effective compliance recording system requires further exploration.

The study achieved a high retention rate, with only control group participants not completing the end-of-study questionnaires. Additionally, the nutritional supplements provided as an incentive to the control group were well-accepted. At baseline, 35% of participants were not taking either folic acid or iodine, and 10% were taking only folic acid. Although 45% of participants were already on a complex supplement regimen, only 15% of the control group declined the trial's supplements, opting to continue with their existing regimen. The knowledge and provision of these supplements seemed effective in engaging the control group, as reflected by 70% reporting a positive trial experience.

Women in the naturopathy group found the intervention acceptable, enjoying the relationship with the naturopath, recommending naturopathy to others with DOR, and considering the advice helpful. Overall, the positive feedback from the participants and the evidence-based approach in developing the naturopathic intervention highlight its potential as a valuable treatment option for women with DOR.

There was no evidence of harm from the naturopathic intervention for women with DOR, but the small sample size and methodology prevents the exclusion of rare events. The few adverse events reported were minor and transient. The weekly surveys were consistently completed by all participants for the trial duration, ensuring thorough and reliable reports of adverse events.

The validation of data-collection questionnaires is fundamental to a feasibility study, especially when self-completed by participants (*Lancaster et al., 2004*). In the present trial, participants found the DASS-21, FertiQol, DGI, IPAQ, PSQI, CEQ questionnaires and self-reported adherence, compliance and adverse events acceptable. The menstrual charts, however, were less well-reported, with 71% (29/41) completing the task. The questionnaires provided most of the relevant information to the researchers; however, an important aspect that was not described was the contribution of the practitioner–patient relationship to the outcomes. It's worth noting that 81% of participants reported enjoying their relationship with the naturopath.

The practitioner–patient relationship has been shown to influence treatment outcomes in various health conditions, with communication styles being a significant factor (*Kelley et al., 2014*; *Świątoniowska-Lonc et al., 2020*). The effect of this relationship on infertility treatment outcomes related to infertility, however, remains underexamined, along with validated measurement instruments (*Godillot et al., 2021*). Further research is warranted to explore the influence of the practitioner–patient relationship on the clinical management of women with DOR.

Participants found that the intervention improved symptoms of depression. Mental health improvements for women with DOR are an important aspect of women's experiences (*Maunder et al., 2024b*), and psychological health of women with infertility is an under-researched area (*Nik Hazlina et al., 2022*); this may be worth exploring in future fully powered trials.

Naturopathy may offer benefits; however, an important question remains: is a future RCT of naturopathy for women with DOR

TABLE 9 INGESTIBLE SUBSTANCES NATUROPATHS PRESCRIBED TO PARTICIPANTS (*N* = 21)

Ingestible substances	Mean dose prescribed per day	Dosage range per day	Actual dose taken per day (%)[a]
Nutritional supplements			
Prenatal multivitamin	1.0	1.0	0.97 (97%)
Fish oils (1 cap = 1g)	3.7 g	2–5 g	2.6 g (70%)
Ubiquinol (1 cap = 300 mg)	780 mg	300–1200 mg	630 mg (81%)
Vitamin D (1 spray = 1000 IU)	4800 IU	0–10,000 IU	2900 IU (60%)
Zinc (1 cap = 30 mg)	51 mg	0–60 mg	39 mg (77%)
Herbal medicines	Mean quantity for 16 weeks[b]	Mean number of formulas[b]	
76% (16/21) were prescribed herbal medicnes	1.138 ml	2.63	989 ml (87%)
Herbal medicines (liquid extracts)	Frequency of use in formulas	Number of patients prescribed herbal medicine	
Asparagus racemosus	27	10	
Angelica polymorpha	17	9	
Actaea racemosa	1	1	
Cinnamomum spp	13	6	
Curcuma longa	18	9	
Dioscorea villosa	4	3	
Ginkgo biloba	30	10	
Glycyrrhiza glabra	4	3	
Paeonia lactiflora	23	11	
Rehmannia glutinosa	25	9	
Matricaria chamomilla	10	7	
Vitex agnus-castus	27	11	
Withania somnifera	35	11	
Zingiber officinale	31	12	

[a] Denominator is mean quantity prescribed.

[b] Denominator is all participants that were prescribed herbal medicines.

justified given the out-of-pocket costs and time involved with naturopathic care? The naturopathic intervention in this trial aligns with the way that naturopathy is provided to women with DOR in the real world (*Maunder et al., 2024c*). Many women with DOR were already incurring out-of-pocket expenses for nutritional supplements, with 76% (31/41) taking supplements before joining the trial. On average, each participant regularly took five supplements per day, with a maximum of 16. It was not investigated whether the supplementation was based on a health professional's recommendation or self-prescribed. Further research is warranted to determine the self-management behaviours of women with DOR seeking pregnancy to enable this vulnerable population to make informed financial decisions.

The present study has some limitations that warrant consideration. First, the lack of blinding could have influenced the responses, particularly for subjective outcomes such as self-reported quality of life, benefits of treatment and compliance. Second, although we attempted to partially control for the non-specific effects of naturopathy by providing a 'stay in touch' telephone call at week 8, the intervention group received a significantly greater amount of attention than the control group, which means it is not possible to determine if the additional attention received was a reason for any improved outcomes, such as reduced depression, in the intervention group. Additionally, because of the small sample size and lack of power, all secondary outcome findings need to be confirmed in an adequately powered trial. Finally, all medical treatment was permitted as part of 'usual care' owing to the time sensitivity in this population; nevertheless, future trials could consider stratifying allocation according to intention to use MAR.

In conclusion, naturopathic intervention for improved pregnancy rates was found to be feasible and acceptable to women with DOR. The recruitment rate indicated that an appropriate and sizeable population is willing to participate in such a trial, and RCT implementation proved feasible across a wide geographical area in Australia. Whole-system naturopathy was found to be acceptable, valuable and safe for women with DOR. Further evaluation of the role of naturopathy in women with infertility and DOR in a fully powered RCT is warranted.

DATA AVAILABILITY

Data will be made available on request.

AUTHORS' ROLES

All authors were involved in the conceptualization and design of the study. AM conducted the study and drafted the manuscript; AM, SA, MA, MC and CE

were involved in data analysis, manuscript revisions and read and approved the final manuscript.

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The authors would like to thank the women who kindly agreed to participate in this study. It is important to acknowledge and recognize that individuals have diverse gender identities. In this study, the terms 'woman' and 'women' were used to refer specifically to all individuals assigned female at birth that were not undergoing any gender affirming hormone therapy. It is not intended to exclude individuals who may identify as a woman but cannot give birth. The purpose of using these terms is to differentiate between the aspects of fertility for those assigned female and male at birth. This trial was supported by Integria Healthcare who provided the herbal medicines and supplements, and BioConcepts who provided additional supplements as an unconditional gift for use in the study. Integria Healthcare is located at Eight Mile Plains, Queensland, 4113 Australia. BioConcepts is located at 19A Guardhouse Road, Banyo, QLD 4014 Australia.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.rbmo.2024.103844.

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