





BMJ Open Protocol of the Fit-For-Fertility study: a multicentre randomised controlled trial assessing a lifestyle programme targeting women with obesity and infertility

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ABSTRACT

Introduction Women with obesity are at a higher risk of infertility as well as gestational and neonatal complications. Lifestyle changes are universally recommended for women with obesity seeking fertility treatments, but such intervention has only been assessed in very few robust studies. This study's objectives are therefore to assess the clinical outcomes and cost-effectiveness of an interdisciplinary lifestyle intervention (the Fit-For-Fertility Programme; FFFP) targeting women with obesity and subfertility in a diverse population.

Methods and analysis This pragmatic multicentre randomised controlled trial (RCT) will include 616 women with obesity (body mass index ≥ 30 kg/m² or ≥ 27 kg/m² with polycystic ovary syndrome or at-risk ethnicities) who are evaluated at a Canadian fertility clinic for subfertility. Women will be randomised either to (1) the FFFP (experimental arm) alone for 6 months, and then in combination with usual care for infertility if not pregnant; or (2) directly to usual fertility care (control arm). Women in the intervention group benefit from the programme up to 18 months or, if pregnant, up to 24 months or the end of the pregnancy (whichever comes first). Women from both groups are evaluated every 6 months for a maximum of 18 months. The primary outcome is live birth rate at 24 months. Secondary outcomes include fertility, pregnancy and neonatal outcomes; lifestyle and anthropometric measures; and cost-effectiveness. Qualitative data collected from focus groups of participants and professionals will also be analysed.

Ethics and dissemination This research study has been approved by the Research Ethics Board (REB) of *Centre intégré universitaire de santé et des services sociaux de l'Estrie—CHUS* (research coordinating centre) on 10 December 2018 and has been or will be approved successively by each participating centres' REB. This pragmatic RCT will inform decision-makers on improving care trajectories and policies regarding fertility treatments for women with obesity and subfertility.

Trial registration number NCT03908099.

Strengths and limitations of this study

- This study has a strong design: a multicentre, two-arm, parallel pragmatic randomised controlled trial comparing the Fit-For-Fertility Programme to usual fertility care, using quantitative and qualitative assessments.
- The primary study outcome of live birth rate at 24 months, and the main secondary outcomes of fertility outcomes and pregnancy or neonatal complications, are strong clinical outcomes pertinent for patients. The study will also provide valuable information on potential cost-effectiveness for individuals and the healthcare system.
- Early involvement of engaged patients, key decision-makers from each province, directors of fertility clinics, as well as professional and public health associations will increase the feasibility of the trial and the potential impact and use of the findings to influence policies and priorities of institutions and governments.
- It is not possible to blind the intervention and data collection since the tested intervention is a lifestyle programme, but the study's primary outcome of live birth is a robust clinical outcome that is not susceptible to bias.
- Self-reported questionnaires may introduce desirability or recall biases, but the study uses tools validated in such setting and these biases should be similar in the intervention and control groups.

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INTRODUCTION

Women with obesity and infertility

Infertility affects approximately 10%–15% of couples in Canada and the rest of North America.¹ According to the International

Glossary on Infertility and Fertility Care, infertility is 'a disease characterised by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with his/her partner'.² For the purpose of this study, subfertility is defined as an infertility with a reasonable probability of spontaneous pregnancy without medical intervention, which excludes couples with sterility or severe infertility (such as bilateral irreversible tubal factor or severe male factor). Medically assisted reproduction (MAR), including ovulation induction, ovarian stimulation, intrauterine insemination and assisted reproductive technology (ART)² are part of the current clinical management of infertility and have become more and more used and effective in helping infertile couples to achieve a pregnancy.³ Unfortunately, these procedures are costly and carry risks for both women and infants. These risks can occur at different stages of ART: ovarian stimulation (ovarian hyperstimulation syndrome, thromboembolism and ovarian torsion), oocyte retrieval (infection and bleeding) and early pregnancy (ectopic or heterotopic pregnancy, and multiple gestations⁴). Although these risks are rare, they can have significant consequences. Furthermore, some studies have suggested that ART procedures may have negative neonatal consequences, such as higher frequencies of alterations in DNA methylation patterns associated with DNA imprinting disorders in children conceived through ART.⁵

Obesity (defined operationally as a body mass index (BMI) ≥ 30 kg/m²⁶), is a known modifiable risk factor associated with female infertility⁷ and the population affected worldwide is high enough for obesity to be recognised as a global epidemic by the WHO since 2000.⁸ The prevalence of obesity has been estimated to be as high as 30% in Canadian and 38% in American populations, respectively.⁹ More precisely, 21% of Canadian women of reproductive age had obesity in 2015.¹⁰ Women who plan to get pregnant are currently more likely to be affected by obesity,¹¹ which can significantly affect their fertility. For instance, a very large cohort study including more than 40 000 couples estimated that women with obesity display a 78% higher risk of having infertility compared with women with a normal BMI (18.50–24.99 kg/m²) (OR with 95% CI: 1.78 (1.63 to 1.95)).¹² Women with obesity are also more likely to develop polycystic ovary syndrome (PCOS), which is the leading cause of anovulatory infertility, affecting 6%–10% of women of childbearing age.¹³ Furthermore, a higher BMI has been associated with reduced pregnancy rates even in women with ovulatory cycles, equating to a 4% decrease in pregnancy rate per kg/m² of BMI increase in women with a BMI ≥ 29 kg/m².¹⁴

Moreover, studies assessing MAR procedures have reported that women with obesity: (i) require higher doses and a longer duration of clomiphene¹⁵ and gonadotrophins^{16–19} to achieve ovulation, (ii) display a lower pregnancy rate per cycle¹⁸ and (iii) are at a higher risk of cycle cancellation^{16 18} and miscarriage.^{20 21} Obesity also

increases the risk of complications during pregnancy, such as gestational diabetes, pre-eclampsia, caesarean section and intrauterine death.^{22 23} In keeping with the Developmental Origins of Health and Disease paradigm, maternal pre-pregnancy BMI and excessive gestational weight gain are consistently associated with the early development of obesity and diabetes in the offspring.²⁴ Obesity in childhood is closely linked to adult obesity,^{25 26} perpetuating the intergenerational cycle of obesity.^{27–29} Adopting a healthy lifestyle before conception and restoring a healthy metabolic environment early during pregnancy likely represents the best approach to break the vicious circle of intergenerational propagation of obesity and diabetes.

Accordingly, targeting women with obesity prior to conception may be essential to reduce the burden of infertility and MAR costs, as well as obesity and cardiometabolic diseases in our societies.

Infertility management in women with obesity seeking fertility treatments

To prevent the adverse effects of obesity on female fertility and on gestational and neonatal health, many organisations have recommended that women with obesity should be assisted, before conception, to lose weight (5%–10% of their initial weight) and adopt a healthy lifestyle, and maintain that healthy lifestyle during pregnancy.^{30–33} Results from a recent systematic review support lifestyle modification prior to ART in women with overweight or obesity.³⁴ The authors pointed out that despite the lack of randomised controlled trials (RCTs) in the area, pre-conception weight loss in women with overweight or obesity can help improve fertility and pregnancy outcomes. Out of the seven RCTs assessing non-surgical methods of weight loss, including some form of lifestyle intervention, the most methodologically rigorous study was a RCT published in the *New England Journal of Medicine* in 2016.³⁵ This study compared 287 women with obesity and subfertility who were randomised to a 6-month structured lifestyle intervention (including six outpatient visits and four telephone consultations with a nurse or dietician) and 285 women assigned to prompt fertility treatments. The lifestyle intervention lasted only 6 months and was not continued during fertility treatments or pregnancy. After a follow-up of 24 months, the lifestyle programme did not improve the live birth rate, but resulted in a significant increase in the rate of spontaneous pregnancies (rate ratio (95% confidence): 1.61 (1.16 to 2.24)) and reduced the need for fertility treatments (rate ratio (95% confidence): 0.78 (0.70 to 0.86)).³⁶ In a follow-up article, the same group of authors observed, from a hospital perspective, an incremental cost-effectiveness ratio (ICER) of €15 845 per additional point of percentage in the healthy live birth rate resulting from the lifestyle programme compared with usual care. The authors concluded that their intervention may be deemed as cost-effective, especially for longer follow-up

timelines, in anovulatory women, women who completed the study or women ≥ 36 years of age.³⁷

Interestingly, in a survey asking women with obesity or overweight and considering pregnancy if they were interested in adopting a healthier lifestyle prior to conception, 91% reported their willingness to participate in a lifestyle programme.³⁸ However, despite the patients' motivation and the international recommendations to encourage women to optimise their lifestyle before starting fertility treatments, most women with obesity do not have access to such targeted lifestyle programmes integrated within their fertility care. Therefore, our objective is to give these women access to the Fit-For-Fertility Programme (FFFP), an interdisciplinary lifestyle intervention, integrated into the fertility clinic care pathway. This programme supports participants in adopting sustainable healthy behaviours, in pre-conception, throughout fertility treatments and during pregnancy. In response to the national priority to improve the quality and costs of reproductive and perinatal care established by our *Canadian network on reproductive and maternal health of women with obesity and infertility*, we will conduct a multicentre RCT assessing the FFFP in women with subfertility and obesity.

Research question and hypotheses

For this RCT, our research question is: Compared with usual care, does the FFFP cost-effectively improve (i) the live birth rate and other fertility outcomes and (ii) pregnancy and neonatal outcomes, in women with obesity and subfertility who seek fertility treatments. We hypothesise that in comparison to prompt initiation of usual fertility care, participation in the FFFP, alone for 6 months and then in combination with usual care for infertility, will: (1) improve the fertility of women with obesity, (2) reduce costs associated with fertility treatments and (3) decrease the occurrence of some complications related to maternal weight during the pregnancy and for their offspring.

Study objectives

The primary objective of this study is to assess the effectiveness of the FFFP on fertility outcomes in a diverse Canadian population of women with obesity and subfertility who are seeking fertility treatments. Secondary objectives are to assess the FFFP's (1) cost-effectiveness, primarily in terms of costs per live birth, as well as other measures of the programme's costs and effectiveness measures, and (2) impacts on maternal and neonatal health.

METHODS AND ANALYSIS

Study design

This study is a multicentre, two-arm, parallel pragmatic RCT comparing the FFFP to usual fertility care, using quantitative and qualitative assessments (ClinicalTrials.gov). More specifically, we developed a pragmatic RCT based on the PRECIS-2 (PRagmatic-EXplanatory Continuum Indicator Summary) principles.³⁹

Patient and public involvement

Our study relies on the early and regular involvement of engaged patients, knowledge users and decision-makers to ensure their appropriation of the results. Policymakers and professional or patient organisations of all relevant provinces provided their support to the project and partnered with the research team to facilitate the feasibility of the trial and dissemination of the results. Importantly, three patient organisations partnered with our team and provided strong support letters: Obesity Canada, the *Association des couples infertiles du Québec* and *Conceivable Dreams*. Engaged patients have been implicated early in the development of this protocol to ensure that the results will be relevant for the target population and that the methods are appropriate for the participants. Two previous participants from the pilot study conducted in Sherbrooke are acting as engaged participants and have participated in each step of the trial's development. Before submission of the grant proposal to the funding agency, they approved the study's research question and its general objectives, as well as the acceptability of the intervention and the burden of research visits. Thereafter, they were regularly consulted by the Sherbrooke research team, and they partnered with the team during dedicated research meetings. Among other contributions, they have given precious input regarding recruitment approaches, data collection tools and timing, intervention upgrades from the pilot study, as well as participants' newsletters. Other fertility clinics have committed to include one or two engaged patients, who will participate at research meetings at each site.

Engaged patients and patient organisations will also be instrumental in disseminating the trial's results to the public, in particular young women with obesity and those with infertility. This will be performed through patient organisations' network, social media, as well as lay public press conferences and 'Café scientifique'-like activities in which our engaged patients will be implicated. Such involvement of decision-makers and patients increases the potential impact on the public and scientific communities, and the use of the study's findings to influence policies and priorities of institutions and governments.

Setting and recruitment

The study will be conducted in seven Canadian fertility clinics from coast to coast and in an ethnically diverse population of women: Olive Fertility Centre in Vancouver (British-Columbia), with its Asian population; Mount Sinai Hospital in Toronto (Ontario) and *Centre hospitalier de l'Université de Montréal*, with large multiethnic communities; *Centre hospitalier universitaire de Sherbrooke* (CHUS) and *Centre hospitalier universitaire de Québec de l'Université de Laval* (CHU de Québec-UL) (Québec), which are smaller centres with mainly a Caucasian population; and Atlantic Assisted Reproductive Therapies Clinic in Halifax (Nova Scotia) that has a Caucasian and Afro-American populations. We are also in the process of recruiting a seventh centre, ideally in the province of Manitoba.

Potentially eligible patients can be approached in one of two ways: (1) by a member within their circle of care (nurse, physician, receptionist, etc) who then provides contact info to research staff, or (2) by responding to an advertisement indicating their interest to learn more about the study. Written informed consent (see online supplemental material) is obtained individually for each patient during the baseline research visit (V0), after a full explanation of the study's protocol and answers to the patient's questions by the research staff, and before any data collection or study procedures. The following screening and baseline data are obtained during this visit: eligibility assessment (inclusion/exclusion criteria), medical history, concomitant medications, patient demographics and a baseline evaluation of study outcomes. Eligibility is confirmed by the site investigator before randomisation.

Participant eligibility

Patients who meet the following inclusion criteria can participate in the study:

1. Being infertile, defined as (a) failure to achieve a clinical pregnancy after ≥ 12 months of regular unprotected sexual intercourse, (b) not conceiving after having attempted ≥ 6 months in women with irregular menstrual cycles or ≥ 35 years of age; or (c) women with an established cause of infertility;
2. Aged between 18 and 40 years (since initiation of fertility treatments should not be delayed in women above 40 years of age); and
3. With obesity (BMI ≥ 30 kg/m² or 27 kg/m² for Asian and Latin American, based on WHO 2004⁴⁰), or with a BMI ≥ 27 kg/m² for women with PCOS. These women display the metabolic consequences of non-PCOS women with obesity at a lower BMI, and benefit more from lifestyle modifications.

Women presenting at least one the following exclusion criteria will not be eligible to enrol in the study:

1. Any uncontrolled medical or mental condition that contraindicates fertility treatments, based on clinical judgement of the fertility specialist;
2. Natural conception is impossible or highly unlikely (eg, bilateral tubal factor, severe male factor defined as a total motile sperm count < 5 million on the most recent partner's seminal analysis), where the only indicated MAR procedures are in vitro fertilisation or donor sperm insemination (this exclusion criteria defines subfertility, such that only subfertile couples are enrolled);
3. History of recurrent spontaneous abortions (> 2 miscarriages at less than 22 weeks of gestation), with evidence of conception (such as positive β -human chorionic gonadotropin (hCG)), within the last 12 months (since these women are more likely to have a defect that cannot be improved by lifestyle);
4. Previously diagnosed uncontrolled eating disorder or major depression that would contraindicate the initiation of a lifestyle intervention;

5. A high level of depressive state, as determined by a score for depression on the Hospital Anxiety and Depression Scale ≥ 15 ,^{41 42} which is not a diagnostic of depression but would also contraindicate the initiation of a lifestyle intervention;
6. Planning for or history of bariatric surgery, which would confound the impact of the lifestyle intervention tested;
7. Planning for or engaging in another lifestyle intervention that would be similar to the intervention tested, for example, including individual visits every 8 weeks or less, which would also confound the impact of the FFFP;
8. Inability to understand the language in which group sessions are provided in the participating centre, that is, French in the province of Quebec and English in other provinces; and
9. Unable to attend research visits at the participating centre for the next 18 months.

Randomisation

Randomisation to the FFFP or control group occurs after completion of the V0 and the eligibility assessment. Group allocation is concealed using online computerised randomisation using REDCap (Research Electronic Data Capture tool hosted at the Université de Sherbrooke)⁴³ with permuted blocks of variable block sizes (2–6), stratified by centre and PCOS status (yes/no). PCOS is an important potential confounder or modifier since it decreases fertility and may affect the response to the lifestyle intervention.¹³ The randomisation list has been generated by an independent statistician and participants are randomised in one of two arms using a 1:1 ratio. The randomisation process is initiated by the site investigator or delegate who accesses the web-based system and confirms patient's eligibility and informed consent. The patient's unique study identifier and open-label study treatment allocation is then automatically and electronically delivered to the local site investigator or delegate.

Following randomisation, the research staff informs the fertility care team of the patient's allocation group. On the one hand, if the participant is randomised to the control group, the fertility care team is informed that their patient can undergo fertility treatments immediately, according to their usual care. On the other hand, if the participant is randomised to the intervention group, the fertility clinic will be notified that the patient has to postpone any MAR procedures for the following 6 months, during which the patient is enrolled in the FFFP. At the end of this first 6-month period, if the participant failed to conceive, the research staff informs the fertility clinic team that the participant can now undergo usual fertility care, in combination with the FFFP.

Interventions

Control arm

Participants randomised to the control group are provided immediate access to the usual fertility care, as

recommended by their fertility specialist, for a maximum of 24 months. This may include lifestyle counselling by their fertility specialist and usual fertility treatments. Since this is a pragmatic trial, they may undergo any lifestyle approaches or consult any professionals they want on their own, but are discouraged to engage in a lifestyle programme similar to the FFFP, as they agreed when recruited for the study, in order to avoid such an important contamination between intervention arms.

Experimental arm

Participants randomised to the intervention group follow the FFFP alone for the first 6 months, then in combination with usual fertility care for an additional 12 months if not pregnant. After these 18 months, usual fertility care can continue to be provided alone for a maximum follow-up of 24 months. The FFFP is also provided throughout gestation for participants who achieve a successful pregnancy. Accordingly, the lifestyle programme is provided for a maximum of 18 months if there is no pregnancy, or otherwise, up to the end of pregnancy or to a total study follow-up of 24 months (whichever comes first).

The FFFP was initially developed based on 2007 Canadian clinical practice guidelines⁴⁴ and the approach implemented by our group at the CHUS obesity clinic,⁴⁵ and was then improved and adapted based on the experience gained from our completed pilot study⁴⁶ and its focus groups. This intervention is aimed at supporting participants to implement progressive and sustainable lifestyle changes. Participants attend 30-min individual sessions with a dietitian and a kinesiologist, respectively, every 6 weeks for the first 6 months, then every 8 weeks for the following 6 months and then every 12 weeks until the

end of the treatment period. These individual meetings take place in person with the participant, or virtually using an authorised system of telemedicine in the event that face-to-face meetings are not possible (eg, due to public health rules such as during the COVID-19 pandemic). Personal remote contact (eg, by phone, email) is offered between in-person meetings. Patients are guided by the dietitian and kinesiologist to formulate SMART goals (Specific, Measurable, Attainable, Realistic and Timely).⁴⁷ These professionals are trained in evidence-based motivational communication skills,⁴⁸ with emphasis placed on how to arm women with the knowledge, motivation and skills to achieve sustainable lifestyle changes. To ensure equitable delivery of the intervention, we will implement an internal quality control and training process. Therefore, after receiving training in motivational communication by our leading expert (KL), each professional will audio-record their first three individual meetings. These recordings will be evaluated by an expert in motivational communication using a coding scheme to verify fidelity. Feedback regarding the professional's application of motivational communication techniques will be provided as needed, and additional recordings may be necessary based on the trainer's assessment. After 6 and 12 months, three more individual sessions are recorded and used to analyse the quality and fidelity of the intervention from a research perspective. Consent for recording individual meetings is a specific question in the informed consent form and participants have the opportunity to revoke their agreement at any time during the course of their participation in the study.

Table 1 Topics of the Fit-For-Fertility's interactive workshops and physical activity sessions

Sessions	Interactive workshops (45 min)	Physical activity sessions (45 min)
1	"Let's get going! Follow the Guide!" <i>Introduction to the Canadian Food Guide</i>	"A step in the right direction!" <i>Walking for fitness (outdoors)</i>
2	"Finding balance" <i>Changes that pay off</i>	"Stay active... even at home!" <i>Weight training exercises at home</i>
3	"Taking charge of your environment" <i>The act of eating</i>	"Step-by-Step!" <i>Step aerobics class</i>
4	"Listening to your body..." <i>Feeling hungry and feeling full</i>	"Bulk up your health!" <i>Muscle building with an elastic band and exercise ball</i>
5	"The label says it all" <i>Food labels</i>	"Stay Zen!" <i>Initiation to yoga</i>
6	"Planning is the key!" <i>Meal planning</i>	"Cardio-muscular walking!" <i>Combined weight training and walking (outdoors)</i>
7	"Thinking about it isn't enough!" <i>Change process and motivation</i>	"Short circuit!" <i>Circuit fitness</i>
8	"Breathe in, breathe out!" <i>Sleep, alcohol and tobacco</i>	"Groove it out!" <i>Aerobic dancing class</i>

Participants also benefit from weekly group sessions divided into two parts of 45 min each⁴⁶ (see [table 1](#) for group sessions' topics): (1) Workshops that cover eight different topics addressing nutritional aspects and relevant healthy lifestyle habits (alcohol, tobacco and motivational issues) and (2) Supervised classes of physical activity where 1 of 8 different types of exercise are practiced. Women are invited to participate in group sessions every week throughout the study, but are required to attend all eight different sessions within the first 6 months. The spouses are highly encouraged to participate in all activities, as lifestyle modification is also important for the partner to improve a couple's fertility.^{49 50}

For women with a confirmed pregnancy, our team schedules a meeting to set new lifestyle objectives specific to pregnancy to promote a healthy pregnancy including optimal gestational weight gain based on the Institute of Medicine guidelines.⁵¹ This meeting can take place during a regular intervention meeting or during the first research pregnancy visit (PV1), whichever comes first.

Data collection

As illustrated in [figure 1](#), research evaluation visits take place in both groups at baseline and every 6 months for a total of 18 months if no pregnancy occurs. Women who become pregnant *within* the first 18 months of follow-up are met at the beginning of their pregnancy (PV1) and at 24–28 weeks of pregnancy (PV2) for measures (see [figure 1](#)). Women who become pregnant *after* 18 months of follow-up do not undergo research visits during their pregnancy. Data collection and measures during these research visits are detailed in [table 2](#).

Participants are instructed to contact the study team between visits or phone calls if they become pregnant or if any relevant situations occur (eg, miscarriage, accident, moving, changing phone number). Importantly, all clinical outcomes are ascertained with participants and their medical records 24 months after participants' randomisation, regardless of the timing of their last research visit and the occurrence of a pregnancy. Pregnancy and neonatal outcomes occurring 24 months after randomisation will not be included in the primary analysis, but are recorded for secondary analyses.

Outcome measures and their assessment

Fertility outcomes

The primary outcome is the cumulative incidence of live birth at 24 months. Secondary fertility outcomes are also collected from medical records at 24 months and include: the rate of biochemical pregnancy (confirmed by a positive serum β -hCG), ongoing confirmed pregnancy (viable pregnancy at ≥ 10 weeks of gestation), spontaneous miscarriage of a confirmed pregnancy (< 22 gestational weeks), multiple gestation, spontaneous pregnancy, pregnancy following MAR procedures, doses of fertility medications, number of MAR and/or ART cycles, number of embryo transfers and complications due to MAR procedures.

Pregnancy outcomes (all secondary outcomes)

Total gestational weight gain, calculated by subtracting weight at the research visit closest to the onset of pregnancy from the last weight available in the antenatal record. Weekly gestational weight gain, calculated by dividing total weight gestational gain by the number of weeks between the first and last measure of weight. Pregnancy complications, which are retrieved from medical records, include gestational diabetes, gestational hypertensive disorders, thromboembolism, preterm birth, late fetal loss, stillbirth and postpartum hospital stay > 7 days.

Neonatal outcomes (all secondary outcomes)

Birth weight, Apgar scores, hypoglycaemic episodes, hyperbilirubinaemia, birth trauma, admission to neonatal intensive care unit and neonatal death (up to 28 days of life), which are retrieved from medical records.

Anthropometric measures and vital signs (all secondary outcomes)

Anthropometric measures are collected at each research visit. Weight is measured with a standard calibrated scale and height is measured with a stadiometer, based on the models available at each centre. Foot-to-foot bioelectrical impedance analysis technology is used to estimate the percentage of fat mass and fat free mass⁵² in most, but not all centres (models depend on each centre). Waist circumference measurement is done with a measuring tape according to the National Institutes of Health.⁵³ Heart rate and blood pressure are measured after a 5 min rest period in a sitting position. Two measurements are taken for waist circumference and vital signs, with the average being used for analyses.

Endocrine and metabolic blood markers (all secondary outcomes)

A blood sample is taken at each research visit to measure different hormonal and metabolic biological markers: luteinising hormone, follicle stimulating hormone, thyroid-stimulating hormone, prolactin, β -hCG, serum progesterone, androstenedione, estradiol, total and calculated free testosterone, sex hormone-binding globulin, glycated haemoglobin, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, cholesterol ratio, glucose, alanine aminotransferase and creatinine (at initial research visit only). All markers are assessed at local laboratories, since they are clinically indicated. Additional plasma samples are shipped to CHUS and stored for future analyses relevant to this study's objectives, when further funding becomes available.

Lifestyle outcomes (all secondary outcomes)

Lifestyle outcomes are assessed at each research visit. Nutritional intake is evaluated using the validated web version of the Food Frequency Questionnaire (FFQ web), referring to the patient's nutritional consumption of the last month. This questionnaire enables to extract data on specific food groups and micronutrients or macronutrients. This questionnaire has been shown to have a moderate validity and a good reproducibility for assessing

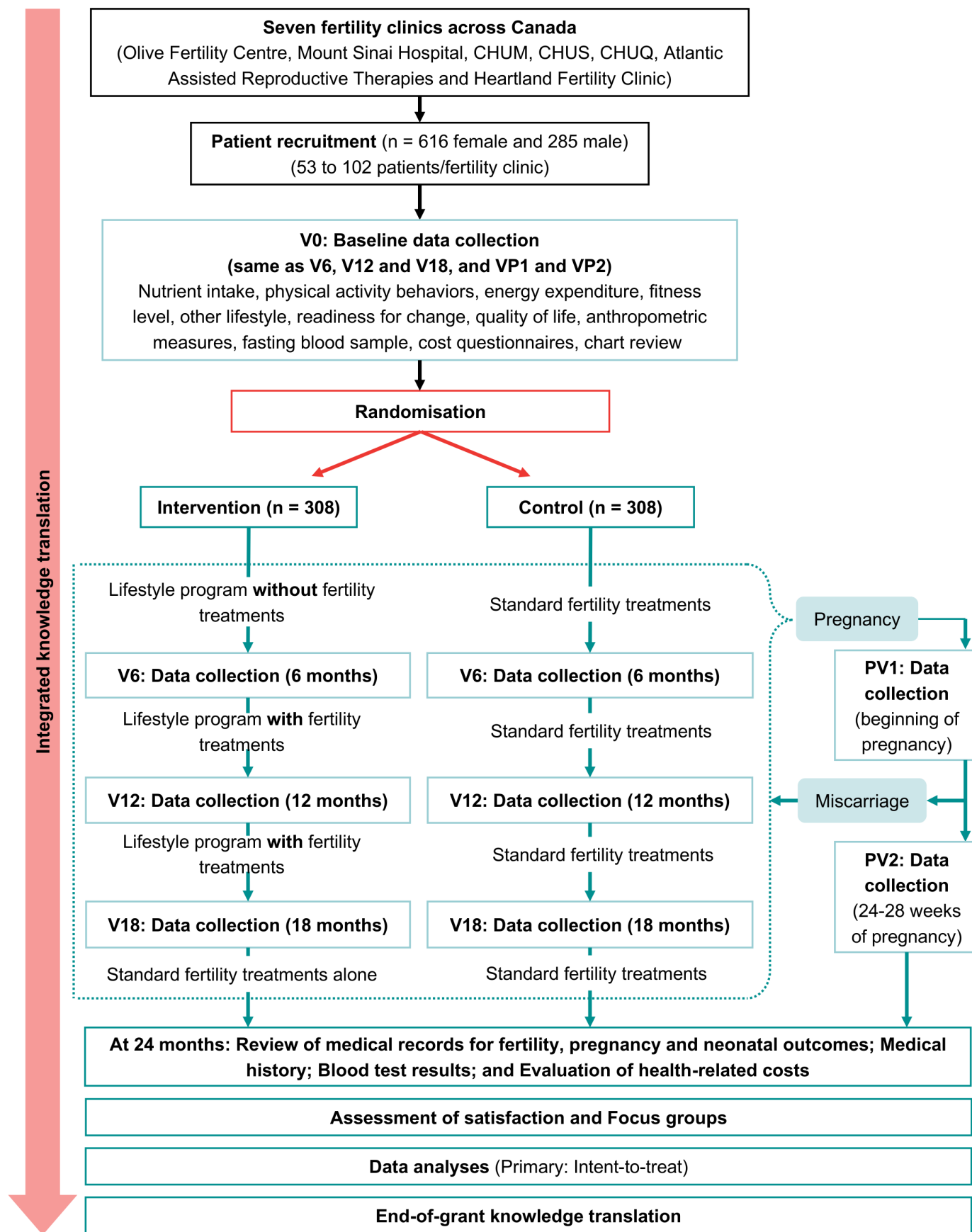


Figure 1 Fit-For-Fertility's study flowchart. CHUM, Centre hospitalier universitaire de Montréal; CHUQ, Centre hospitalier universitaire de Québec; CHUS, Centre hospitalier universitaire de Sherbrooke.

**Table 2** Research visits and data collected

	V0	V6	V12	V18	PV1	PV2
Informed consent	●					
Physical examination (anthropometry, blood pressure and heart rate)	●	●	●	●	●	●
Concomitant medications	●	●	●	●	●	●
Blood sample						
Fasting levels of sex steroids	●	●	●	●		
FSH, LH	●	●	●	●		
TSH	●	●	●	●	●	●
Prolactin	●	●	●	●		
β-hCG	●	●	●	●	●	
ALT	●	●	●	●	●	●
HbA1c	●	●	●	●	●	●
Glucose	●	●	●	●	●	●
Lipids	●	●	●	●		
Creatinine	●					
Extra samples shipped to the coordinating site (Sherbrooke, Quebec)	●	●	●	●	●	●
Initial Medical Questionnaire	●					
Actual Health Status Questionnaire		●	●	●	●	●
FertiQoL	●	●	●	●		
HADS	●	●	●	●	●	●
IPAQ	●	●	●	●	●	●
Readiness to Change Questionnaire	●	●	●	●	●	●
PSQI	●	●	●	●	●	●
Socio-demographic Questionnaire	●					
Patient's Costs Questionnaire		●	●	●	●	●
SF-6D V.2	●	●	●	●	●	●
FFQ web	●	●	●	●	●	●
Fitbit & Fitbit Journal	●	●	●	●	●	●
6-minute walking test	●	●	●	●	●	
Participant's Satisfaction Questionnaire				●		●
AEoSI and SAE review	●	●	●	●	●	●

AEoSI, adverse events of special interest; ALT, alanine aminotransferase; FertiQoL, Fertility Quality of Life questionnaire; FFQ, Food Frequency Questionnaire; FSH, follicle-stimulating hormone; HADS, Hospital Anxiety and Depression Scale; HbA1c, glycated haemoglobin; IPAQ, International Physical Activity Questionnaire; LH, luteinising hormone; PSQI, Pittsburgh Sleep Quality Index; PV1, first pregnancy research visit (beginning of pregnancy); PV2, pregnancy research visit at 24–28 weeks of gestation; SAE, serious adverse events; SF-6D V.2, Short Form-6 Dimensions – version 2; TSH, thyroid-stimulating hormone; V0, baseline research visit; V6, V12, V18, research visits at 6, 12 and 18 months post-randomisation, respectfully; β-hCG, human chorionic gonadotropin.

nutrient intakes in healthy adults.⁵⁴ Participants complete the questionnaire at the research centre at their first research visit to ensure good understanding of the questions. For subsequent research visits, participants have the possibility to receive a link to complete the FFQ web electronically from home. Sleep duration and quality are evaluated by the Pittsburgh Sleep Quality Index questionnaire, which has been shown to have a strong reliability

and validity, as well as a moderate structural validity in the context of screening for sleep dysfunction.⁵⁵ The International Physical Activity Questionnaire—short version—is used to assess physical activity practice over the past 7 days: it was shown to have a good repeatability of data and is as reliable as other self-administered physical activity questionnaires.⁵⁶ Furthermore, participants are asked to wear after the research visit a Fitbit Flex 2

monitor during seven consecutive days, 24 hours/day, in order to objectively assess physical activity levels (energy expenditure, number of steps, distance walked, time spent being inactive, lightly active, active and very active), as well as sleep data (minutes spent asleep, awake and restless (when moving while sleeping)). Fitbit devices have been shown to accurately estimate the daily number of steps and the time spent in bed and sleeping, while overestimating the time spent doing highly intense activities.⁵⁷ However, data extracted will be mainly used to assess the change of physical activity levels and sleep over time and not whether physical activity recommendations are met. This estimation bias should be consistent at each measurement time point and will be adjusted for baseline measures. The participant's physical fitness level is assessed using the 6-minute walk test, which has shown to be a simple, safe and low-cost test to assess the effect of an intervention on the physical performance and walk capacity beyond weight loss.⁵⁸ Other lifestyle habits, such as alcohol, tobacco and drugs consumption, are measured by a study-specific self-reported questionnaire.

Quality of life (secondary outcome)

Participants' quality of life specifically related to infertility and its treatments are assessed using the Fertility Quality of Life questionnaire.⁵⁹ Moreover, the Short Form-6 Dimensions—V.2 is used to determine quality-adjusted life years (QALY), which is an important variable for the economic evaluation of the intervention, and to assess the general quality of life of our participants, as well as the impact of our intervention on dimensions of quality of life.

Patients' perceptions and satisfaction (all secondary outcomes)

Based on experience from previous studies,^{46 60 61} we will evaluate the expectations, perceptions and satisfaction towards care provided for fertility and weight management in all participants with a questionnaire. These aspects will be further assessed on a small sample (from both groups) using focus groups. The satisfaction questionnaire is given at the 18-month research visit (V18) or at the second pregnancy research visit (PV2) if pregnant. Focus groups will take place at two time points: (1) after completion of the study by half of the participants and (2) close to the end of the trial. A total of 168 patients (27% of all participants) will participate in the focus groups across all seven centres, each centre evaluating two separate subgroups of six patients from the intervention and control groups. The number of participants for the second series of focus groups may be adjusted to reach data saturation. See below under 'Methodology and analyses of qualitative substudy' for more details.

Health-related costs (secondary outcomes)

Data are collected from both the patient and the health-care system perspectives for each mother/child dyad. Costs of interest include costs related to the FFFP, fertility treatments, adverse events or complications,

pregnancy-related visits and hospital admissions, and patient out-of-pocket expenses. Data collection for this component will be done through patient questionnaires, charts reviews, administrative data and interviews with healthcare providers and fertility clinic staff for the description of care procedures.

Medical history and physical health (all secondary outcomes)

A study-specific self-administered questionnaire will be used to evaluate participant's relevant medical history, use of medications or natural products, and physical health during daily activities. It will be possible with the data of this questionnaire to use the Edmonton Obesity Staging System, which has been shown to be an effective classification tool for obesity risk assessment, including in the context of obesity and infertility.⁶²

Data management, monitoring and quality assessment

Research measures and outcomes are recorded through printed or online versions of the questionnaires and paper case report forms at each relevant time point. These are checked for integrity by each site's research assistant before being entered into the centralised web-based database REDCap.

The central coordinator at the CHUS is responsible for training of the research staff and health professionals (dietitians and kinesiologists), and the monitoring at all centres. The central coordinator is also responsible for ensuring that patient safety, study procedures and data collection are performed at each centre according to the research protocol and Good Clinical Practice guidelines.⁶³ The central coordinator sends regular queries to site coordinators to resolve discrepancies identified in the database and performs regular on-site visits. These visits will begin after the site research teams have recruited their first 35 participants (corresponding to one-third of participants to be recruited per site). Then they will be held at every 6-month intervals to assess protocol adherence, intervention standardisation, as well as data completeness and quality. During on-site monitoring visits, approximately 10% of participants' records will be reviewed. Concordance with the original data entered by the site will be assessed using the Cohen's kappa statistics. A kappa coefficient below 0.60 for one site at the time of a visit, which is considered as less than a moderate concordance,⁶⁴ will require repeating the training of research staff at this site and, if necessary, revising all records of participants who completed the study at this site, if possible.

The trial steering committee of this projects includes J-PB, RB, AG, EG, KW, BC-M, A-SM, CK-N, M-HP, BT and their key research team members. An advisory committee is also in place and includes J-PB, WF, FG, M-FL, KL, TP, A-SM, S-MR, KA, NC, MS, SL, Becky Attenborough, now retired from the Reproductive Care Program of Nova Scotia, Celine Braun, president of the *Association des couples infertiles du Québec*, Rahda Chari, now retired from the Maternal Newborn Child & Youth Strategic



Clinical Network, Alberta, Anne Hayes from the Ministry of Health and Long-Term Care of Ontario, Tamil Kendall, past provincial executive director of perinatal services BC, Martine Pageau, *Directrice du sport, du loisir et de l'activité physique* at *Ministère de l'Éducation et de l'Enseignement supérieur du Québec*, Daniel Riverin, past director of Mother-Child Services of Quebec Ministry of Health and Danielle Xavier, past president of Conceivable Dream. The steering and advisory committees meet periodically to support the coordination of the Fit-For-Fertility study, and their implication had already started at the protocol design stage.

Safety measurement

Due to the relatively short duration of recruitment and follow-up of participants, it will not be relevant to perform formal interim efficacy analyses for futility or superiority and interim safety analyses. Furthermore, it is very unlikely that the proposed lifestyle intervention, which is already recommended during preconception and pregnancy in women with obesity, would cause any safety issues. For these reasons, a Data and Safety Monitoring Board will not be required for this trial, and no interim analyses will be performed. However, adverse events of special interest (AEoSI) and serious adverse events (SAE) will be closely monitored throughout the study (see [box 1](#)). These potential events will be evaluated according to their causality and severity. Furthermore, after randomisation of the first 50 patients, the trial's steering committee will produce a quarterly blinded report of AEoSI and SAE for each treatment group, including the grades of causality with the intervention. If SAE occur, these events will be reported to the coordination centre and local Research Ethics Board (REB), as well as the central REB of the Province of Quebec.

Statistical analyses and sample size

Sample size calculation

Experts from our *Canadian network on reproductive and maternal health of women with obesity and infertility* agreed that for a study using a lifestyle intervention and following intent-to-treat (ITT) principles, the minimal clinically important difference in the trial primary outcome, that is, cumulative live birth rates, would be 15% between groups. Therefore, a sample size of 293 women per group is required to detect a 15% absolute difference between groups, with a power of 95% and alpha level of 5%, from an estimated live birth rate of 35% in the control group (based on our previous pilot RCT⁴⁶) to 50% in the intervention group (nQuery Advisor V.4.0). Assuming a withdrawal rate of 5% (eligibility criteria violation and loss to follow-up), the total recruitment target is 616 women. A 95% power is sufficient for most of our secondary outcome analyses. To recruit a total of 616 participants in 18 months, the two clinics with smaller practices (CHUS and *Centre hospitalier universitaire de Québec* (CHUQ)) will need to recruit 53 participants (ie, 39 per year), and the other five clinics will have to recruit 102 participants (ie,

Box 1 Adverse events of special interest (AEoSI) and serious adverse events (SAE) monitored during the study

AEoSI

- ▶ Clinically significant injury (requiring consultation or limiting activities) occurring during exercise, that is, a planned physical activity with the purpose of improving or maintaining physical fitness.
- ▶ Spontaneous miscarriage (spontaneous loss of a pregnancy before 22 weeks of gestation).
- ▶ Ovarian hyperstimulation syndrome.
- ▶ Multiple gestation.
- ▶ Gestational diabetes requiring pharmacological treatment, usually insulin.
- ▶ Gestational hypertensive disorder (gestational hypertension, pre-eclampsia or eclampsia).
- ▶ Thromboembolic clinical event during pregnancy.
- ▶ Preterm birth (occurring after 22 weeks and before 37 weeks of gestational age).
- ▶ Newborn small for gestational age (birth weight <10th percentile of the sex-specific birth weight for gestational age reference).
- ▶ Newborn large for gestational (birth weight >90th percentile of the sex-specific birth weight for gestational age reference).

SAE

- ▶ Antenatal clinically significant uterine bleeding (requiring admission or blood transfusion).
- ▶ Late fetal loss, that is, fetal death between 22 and 28 weeks of gestational age.
- ▶ Stillbirth (>28 weeks of gestational age).
- ▶ Neonatal death (between childbirth and before 28 days of life).
- ▶ Newborn with severe congenital malformation (causing a functional handicap).
- ▶ Admission of newborn to the neonatal intensive care unit.
- ▶ A medical complication that prolongs mother's postpartum hospital stay >7 days.

68 per year). These recruitment rates are feasible given the data from our pretrial survey of participating fertility clinics that showed that smaller practices (CHUS and CHUQ) evaluate 80 to 315 new women with obesity per year, and larger practices, between 265 and 810.

Statistical analyses of quantitative data

The primary outcome is 24-month live birth cumulative incidence and the primary analyses of interest will be ITT, including all randomised participants with available data and no violation of eligibility criteria. The ITT analyses will be supplemented by per-protocol analyses that will exclude women who dropped out of the study during their first 6 months in both groups, that is, who signified their desire to stop participating in the study and/or intervention visits, or were unreachable from that period up to the end of the trial. The per-protocol analyses will keep all women who persevered in the study for at least 6 months and were therefore appropriately exposed to the intervention (intervention group) and adherent to the 6-month study visit (both group). The 24-month cumulative incidence of live birth will be compared between the two arms using the Mantel-Haenszel test with stratification by centre and PCOS status. This analysis will be

supplemented by a survival analysis (logrank test) where the time to live birth will be used. Randomised groups will be examined at baseline to ensure demographic and clinical data are comparable. If substantial imbalance is found, which is very unlikely, additional analyses will be carried out to assess the potential confounding effects of this imbalance, using multiple logistic regression and Cox proportional hazards model. Similar analyses will be used for the other clinical outcome variables that are categorical. Continuous outcome variables will also be compared between groups based on either ITT or per-protocol analyses, using linear mixed models with repeated measures.

We will also analyse the impact of the FFFP on lifestyle and anthropometric outcomes, as well as other outcomes measured during a research visit, at 6 months (including research visits occurring 6 ± 1 months after randomisation), as frequently reported in previous and similar trials. For these analyses, continuous variables will be compared between groups using unpaired t-tests and categorical variables will be examined using χ^2 tests. Missing data due to missed research visits or incomplete data collection will not be imputed, due to the relatively small sample size, such that these analyses might be subjected to non-random missing data differing between groups. Therefore, these tests will be corrected for potential baseline imbalances and confounding effects as mentioned above. Variables that are not normally distributed will be mathematically transformed to fit a normal distribution allowing their use in these models. Subgroup analyses will be performed for all outcomes based on baseline age, level of obesity (BMI ≥ 35 vs < 35 kg/m²), ethnic origins, socioeconomic status, the cause of subfertility and PCOS status. A 5% level of significance will be used for all analyses.

Economic evaluation

The economic evaluation of the FFFP represents the second objective of this study. The primary economic analysis will be based on the ICER, using live birth as the primary effectiveness outcome. As a secondary measure of cost-effectiveness, QALYs will be calculated from the SF-6D V.2,^{65 66} using the algorithm developed by Mulhern *et al.*⁶⁷ QALYs will help in considering the aspect of health-related quality of life affected by weight reduction, healthy lifestyle and psychological impacts of subfertility. A 1.5% discount rate will be considered for periods higher than 1 year and sensitivity analysis will be performed.⁶⁸ To estimate the CI on the difference in costs, we will perform non-parametric analyses with 5000 bootstrap replications. We will also perform cost-effectiveness acceptability curves to compare the cost-effectiveness thresholds for different costs per unit gain.^{68 69}

Methodology and analyses of qualitative substudy

In addition to the simple satisfaction questionnaire, an in-depth, qualitative iterative exploration of patient's perceptions of the FFFP and medical care will be performed. Purposive sampling will be used to create the two sub-groups in each clinic, based on the technique

of critical incidents using patients' characteristics (levels of satisfaction with their care based on questionnaires, fertility or pregnancy outcomes, loss or gain of weight during follow-up, ethnic group, etc.). A semi-structured interview guide will be used for the focus groups, tailored to each trial group, with open-ended questions adapted from results of previous studies on similar topics.⁷⁰ The 90-minute focus group meetings will be led by a facilitator who will encourage participation and discussions.^{71 72} An experienced observer from our research group will participate remotely from Sherbrooke: he will take notes and support the facilitator, by asking follow-up questions, for example. Data will be analysed as soon as possible by a member of the research team, using Miles, Huberman and Saldana's method. The analysis of the content of the focus groups as they are conducted will help enrich the subsequent focus groups (iterative approach).⁷³ A preliminary analysis grid with various categories based on our previous work will be used, to which emerging categories will be added successively. Regular discussions with the research team will take place during the analysis process to promote a comprehensive understanding of the material collected.

After the trial completion, health professionals' perceptions, self-efficacy, inter-professional collaboration and satisfaction toward obesity management will be evaluated through a taped-recorded semi-structured focus group interviews in each clinic, as we have previously done.^{46 60 74} Discussions among physicians, nurses, dietitians, kinesiologists, clinics' administrative personnel and directors will be encouraged. These focus groups will be performed and analysed using the same methods as described above for patients.

DISCUSSION

In this paper, we present the research protocol for a multi-centre pragmatic RCT assessing clinical and economic outcomes of an interdisciplinary lifestyle intervention targeting women with subfertility and obesity (the Fit-For-Fertility programme) that takes place 6 months before initiating fertility treatments and, for the first time, continues in combination with usual fertility care as well as during pregnancy. This study will highlight the effectiveness, cost-effectiveness and transferability of such a programme in a diverse population.

Obesity has been shown to negatively impact on women's reproductive capacity by reducing chances of pregnancy, with or without the help of fertility treatments.^{12 16 18 19} Women with obesity are also at a higher risk of complications during pregnancy. Interventions supporting changes in lifestyle habits and a moderate weight loss of 5%–10% of the initial weight are highly recommended for women who are trying to conceive.^{31–33} Unfortunately, there is little evidence from large and of good quality RCTs in this population supporting this recommendation. To our knowledge, there is only one published RCT (the LIFESTYLE study) evaluating the impacts of a 6-month



lifestyle intervention on fertility outcomes among a general population of women with obesity and subfertility, not specifically affected with PCOS.³⁵ Although the authors did not observe an improvement in their primary outcome (vaginal birth of a healthy singleton) with their lifestyle intervention as compared with usual care, they reported a higher proportion of women in the intervention group achieving a spontaneous pregnancy (26.1% vs 16.2%, relative risk with 95% CI: 1.61 (1.16 to 2.24)) and a reduced total number of treatment cycles. Our trial will therefore contribute significantly to the actual knowledge and levels of evidence in the literature.

Although this study uses a robust methodology, as all studies, it has a few limitations. First, it is not possible to blind the intervention and data collection, either to the participants nor the professionals (research or clinical), since the tested intervention is a lifestyle programme. Although a blind research study adds robustness and limits potential bias, we do not think this represents an important stake, because the study's primary outcome is life birth, which is a robust clinical outcome that is not susceptible to bias. Second, data collection is done mainly using self-reported questionnaires that can result in a desirability bias. However, most of the questionnaires used have been validated and used in previous studies, and the bias should be similar in the intervention and control groups. Additionally, self-reported questionnaires may introduce a recall bias when patients have to report on previous events (eg, costs, nutritional intake in the last month). In that perspective, clear and detailed instructions are given to patients at each research visit to assist them in completing the questionnaires to the best of their ability. Thirdly, there may be a degree of diversity in the FFFP delivery due to the multicentre nature of the study. In the context of a pragmatic RCT, this diversity would in fact, reflect the real-world reality of programme implementation in different fertility clinics. While we consider this aspect to be a strength contributing to the generalisability of the results, it could also result in a variability in the efficacy of the intervention at each centre. To mitigate this concern, formal training is provided to all health professionals regarding motivational interviewing techniques, with coaching for the first meetings with participants until the professional masters these skills appropriately. Fidelity of the proper use of motivational communication in real clinical settings will be monitored throughout the study and corrective measures will be initially suggested to professionals, if needed. Furthermore, some standardisation in administering the core concepts of the FFFP is provided to health professionals beforehand to ensure that the interventions are as effective as possible.

Despite its limitations, this study is highly relevant and uses a robust study design. The multicentre setting allows our work to be more generalisable, because of the diversity in the subpopulations and healthcare systems enrolled. The slight differences in provincial healthcare systems in Canada will allow us to examine the potential of the FFFP

to be implemented in various healthcare contexts. The proposed study relies on early involvement of engaged patients, key decision-makers from each province, directors of fertility clinics, as well as professional and public health associations, which will increase the potential impact and use of the findings to influence policies and priorities of institutions and governments. The results of our multicentre RCT will have a major scientific impact since they will provide important data on the importance of a lifestyle programme supporting women with obesity seeking fertility treatments. We believe our work will promote better fertility outcomes and response to ART as well as contribute in achieving a healthy pregnancy and giving birth to a healthy baby. This study will also provide valuable information on potential cost-effectiveness for individuals and the healthcare system. Therefore, the Fit-For-Fertility study has the potential to improve the care trajectory of women with subfertility and obesity seeking fertility treatments, and do so at an acceptable cost both for patients and government-funded providers.

Ethics approval and consent to participate

This research study has been approved by the Research Ethics Board (REB) of *Centre intégré universitaire de santé et des services sociaux de l'Estrie – CHUS (CIUSSS de l'Estrie – CHUS)* (research coordinating centre) on 10 December 2018 (approval number: MP-31-2019-2802). The central REB of *CIUSSS de l'Estrie – CHUS* acts as the central REB for centres in the Province of Quebec and individual ethics approval has been obtained for all participating centres in the other provinces (IWM Research Ethics Board (IWK-REB); approval number: #1025047, Office of Research Ethics from the University of British Columbia; approval number: H18-03597, Research Ethics Board from Mount Sinai Hospital; approval number: 19-0317A), and will be obtained for the seventh centre to be recruited. Ethics approval will be maintained annually. Informed consent is obtained from participants before beginning any research procedure and supported throughout their participation in the trial. Participants may withdraw at any time during the study without impacting their regular medical care. If the study participant decides to leave the study, the information that was collected will still be available in helping answer the study's research questions unless the participant provides written documentation of her wish to have the data removed. All personal health information will be treated in a confidential manner with respect to its collection, use and disclosure. Participant names or potentially identifying personal health information will not leave the institution. A master list that links participant identifiers to their unique participant number will be maintained at all study sites, stored separately from all other study records according to local institutional policies, and locked by key or password.

Consent for publication

Not applicable.

Trial status

Due to the widespread public health rules and restrictions implemented in the province of Quebec from March 2020 due to the COVID-19 pandemic, the RCT has experienced considerable delays in the initiation of the study in each centre. Furthermore, one centre located in the province of Alberta had to withdraw from the trial for considerations related to the pandemic. Recruitment has begun in Sherbrooke, Quebec, with its first randomisation in May 2019 (n=33 as of November 2021), Québec City, Quebec, in February 2020 (n=14), Toronto, Ontario, in May 2021 (n=1) and in Montreal, Quebec, in November 2021 (n=1). The centre in Halifax has not yet begun recruiting because of COVID-19 restrictions in its province. Other centres are ready and allowed to start recruiting at this time. We are also in the process of recruiting a seventh centre in the province of Manitoba.

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Contributors J-PB is the senior author of the manuscript, he designed the study and obtained funding as principal investigator of the trial; and MB wrote the first draft of the manuscript in collaboration with MG, FJ-D and J-PB. Authors have made substantial contributions to the conception or design of the trial (J-PB, BC-M, M-FL, A-SM, S-MR, KL, KA, TP, FG, M-HP, FJ-D, RB, MS, BT, NC), contribute or will likely contribute to the acquisition of data for the study (J-PB, MG, BC-M, A-SM, FG, M-HP, FJ-D, RB, AG, EG, CK-N, KW, SL, BT), and/or will likely contribute to analysis or interpretation of future data (J-PB, BC-M, M-FL, A-SM, S-MR, KL, KA, TP, FG, M-HP, RB, WF, EG, CK-N, MS, BT). All authors revised critically this manuscript for intellectual content, approved the version to be published and agreed to be accountable for all aspects of the work.

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