

BMJ Open ProVag: the effect of oral probiotics on the vaginal microbiota composition in women receiving medical assisted reproduction in a Dutch fertility clinic – protocol of a randomised, placebo-controlled, double-blind study

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ABSTRACT

Introduction Differences in the profile of the vaginal microbiota (VMB) have been associated with pregnancy rates after medical assisted reproduction (MAR) such as in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI). Monitoring the VMB profile of IVF patients creates an opportunity to identify the best window for IVF treatment and embryo transfer. The ReceptiVFity test is a predictive test that assesses the chances of becoming pregnant in women undergoing IVF treatment based on the VMB composition. A VMB profile dominated by beneficial strains, most notably *Lactobacillus* species, is associated with increased pregnancy chances. However, to date, limited evidence is available on the effect of active modification strategies to facilitate the modulation of the VMB profile to help restore a VMB dominated by *Lactobacillus* species.

Methods and analysis This is a randomised, placebo-controlled, double-blind intervention study. The study will involve 1:1 randomisation to one of the two arms: oral probiotic or placebo. Vaginal and rectal swabs will be collected at intake and 4, 6 and 8 weeks after the start of the treatment. Our objective is to determine if oral probiotic treatment improves the VMB profile of IVF patients from a low to a medium/high ReceptiVFity score, compared with placebo treatment. Secondary outcomes are: the potential of the bacterial strains in the oral probiotic to be detected in the vaginal tract and/or in the gut, and if the treatment leads to an increased ongoing pregnancy rate after IVF.

Ethics and dissemination Ethical approval was obtained by the local medical ethical review committee at the Maastricht University Medical Centre. Findings from this study will be published in a peer-reviewed scientific journal and presented at one or more scientific conferences.

Trial registration number CCMO NL81210.068.22, registered 25 September 2023.

INTRODUCTION

Infertility is a serious issue of public health relevance that affects one in six couples

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The study design of a randomised, placebo-controlled, double-blind trial is the most accurate study design to address the research question.
- ⇒ The IS-Pro technique provides detailed information on bacterial species composition comparable with 16S rRNA gene sequencing with the benefit of less costs, less labour intensity and more rapid results.
- ⇒ Study follow-up is limited to 12 months, and so the study will not be able to evaluate potential longer-term impact on the offspring.

worldwide.^{1 2} In over 30% of the affected couples no underlying cause is known, leading to further suffering and stress.³ To date, the most valuable option for infertile couples is medical assisted reproduction (MAR), such as in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI). Marked progress in the field has helped to improve the cumulative success rate of IVF procedures up to 30% per started IVF cycle.⁴ Yet, failure rates remain a concern as they impose a heavy toll on couples, the healthcare system and the costs thereof.

A key issue in the success of an IVF or ICSI treatment is the implantation of the embryo. This depends on the quality of the embryo and the ability of the endometrium to accept embryo implantation. There is a cross-talk between the embryo and the endometrium with diverse factors involved, which can lead to a successful ongoing pregnancy. Recently, the role of the vaginal microbiota (VMB) in embryo implantation has gained attention. The VMB consists of the collective microorganisms that inhabit the lower female genital



tract. A healthy VMB is known to be of low species richness (number of species) and evenness (relative abundance of species). Furthermore, a healthy vaginal microenvironment has been repeatedly associated with a VMB dominated by *Lactobacillus* species and characterised by a low pH (acidity).⁵ An imbalance in the composition of the VMB, such as depletion of *Lactobacilli* and increased species richness, is referred to as vaginal dysbiosis and is associated with an increase in local pH.^{5–6} Such disruptions in the VMB and local pH have been associated with various adverse genital and reproductive conditions, such as infertility, adverse pregnancy outcome and preterm birth.^{7–9}

Indeed, a recent meta-analysis identified low *Lactobacillus* VMB with female infertility based on fifteen included studies.¹⁰ Looking specifically into patients undergoing IVF treatment, multiple studies suggest that abnormal VMB may be associated with poor reproductive outcomes in these patients, such as unsuccessful embryo implantation and lower pregnancy rates.^{11–14} Moreover, VMB mostly composed of *Lactobacilli* was associated with IVF-embryo transfer (ET) success rates and pregnancy rates in women suffering from recurrent implantation failure (RIF).^{15–18}

Current innovations in MAR offer clinicians the possibility to monitor VMB profiles in IVF patients in order to identify the best window for IVF treatment and ET. One such innovation is the Conformité Européenne (CE)-marked ReceptIVFity test, a predictive test that assesses the chances of becoming pregnant in all women undergoing IVF treatment based on the VMB composition.¹⁸ By characterising the bacterial communities in the vagina of women starting their IVF treatment, the ReceptIVFity test can result in a high, medium or low vaginal profile score. With a high score, the chance of pregnancy following a first IVF treatment is 52.6%. The pregnancy chance with a medium score is 23.6% and with a low score 5.9%.¹⁸ Four parameters are used to predict failure to become pregnant after IVF treatment, hence resulting in a low profile score: relative *Lactobacillus* load <20%, and/or relative load of *L. jensenii* >35%, and/or presence of *G. vaginalis* IST1 and/or relative proteobacteria load >28%. This predictive algorithm has been developed based on VMB profiling of 192 women who underwent a fresh ET and was subsequently validated in an external cohort of 50 women undergoing IVF.¹⁸

Naturally, the VMB profile tends to shift between low, medium and high ReceptIVFity profiles over time with a spontaneous conversion to a beneficial profile in the majority of initially low profile patients over a time period of 1–3 months.¹⁹ While little options currently exist for active modulation of the VMB in patients with vaginal dysbiosis, there may be a window of opportunity for *Lactobacillus*-containing probiotics to actively help restore a VMB profile dominated by *Lactobacillus* species, supportive for implantation and subsequent pregnancy. Such a solution will ultimately assist and empower patients and support them in the journey towards childbearing.

In this randomised, placebo-controlled, double-blind, intervention study, we will investigate whether the VMB can be modulated, and physiological pH maintained or restored, using oral probiotics in a population of patients undergoing IVF compared with a placebo treatment. Secondary outcomes of interest are: the potential of the bacterial strains in the oral probiotic to be detected in the vaginal tract and/or in the gut and if the treatment led to increased ongoing pregnancy rates after IVF. Oral probiotic formulations, qualified as food supplements by the current European regulations,²⁰ do not require drug approval and can quickly become implemented in practice. In addition, oral intake allows probiotic bacteria to reduce pathogen migration towards the vagina at the level of the gut, which might increase their effectiveness. Moreover, multiple clinical studies have shown the capacity of oral probiotics to modulate the VMB. Several oral probiotics have shown to positively modulate the VMB and increase *Lactobacilli*, taken alone as well as in conjunction with antibiotics.^{21–26}

METHODS AND ANALYSIS

Trial design

This study is a randomised, placebo-controlled, double-blind intervention study with two study arms. Patients will either receive 3 grams of oral probiotics or a placebo treatment daily.

The Standard Protocol Items: Recommendations for Interventional Trials checklist has been used when writing our report.

Study settings

This study will be carried out in the fertility clinic of the Maastricht University Medical Centre+ (MUMC+) in the Netherlands. Recruitment is expected to begin in November 2024 and continue for a period of about 24 months or until the target number of inclusions has been achieved. Women undergoing IVF treatment (regardless of the cycle number) will be invited to participate and will be screened for inclusion and exclusion criteria. After informing eligible participants, an informed consent form will be obtained to confirm they are willing to participate in the study (online supplemental file S1. Participant consent form). Then, they will be randomised for the two possible treatment arms, the oral probiotic or the placebo.

Study population

All IVF patients attending the MUMC+ Fertility Clinic, and undergoing IVF treatment (regardless of the cycle number), will be invited to participate and will be screened for inclusion and exclusion criteria. Inclusion criteria are non-smoking females, age between 18 and 43 years, with primary or secondary infertility with an IVF indication, low VMB profile as measured by the ReceptIVFity test and written informed consent (online supplemental file S1. Participant consent form). Exclusion

criteria are use of oral/vaginal antibiotics during a 6-week period before (and up to) enrolment, use of other oral or vaginal probiotics at enrolment and during the study, use of hormonal treatment other than for IVF, pregnant at enrolment, genital symptoms at enrolment, history of adverse reaction/allergy to any of the content in the probiotic or placebo, serious illnesses or hospitalised or immune compromised specified to: usage of immune suppressants, immune deficiency disorders and disorders with a disrupted intestinal barrier, undergoing preimplantation genetic testing (PGT) for hereditary disorders.

Due to the previously observed willingness of patients to contribute to scientific studies on treatment to improve fertility, it is expected that the majority of eligible patients is willing to participate.

Primary objective

The primary objective of this study is to investigate whether oral probiotic treatment changes the VMB profile score of IVF patients from low to medium/high, measured by the ReceptIVFity test, more often compared with a placebo treatment after 8 weeks of treatment.

Secondary objectives

The secondary objectives that will be studied are:

- ▶ Can bacterial strains in the oral probiotic treatment be detected in the vaginal tract and/or in the gut?
- ▶ Can changes in the microbiome be seen already after 4 and 6 weeks of treatment, and how does this relate to the placebo treatment group?
- ▶ Does oral probiotic treatment lead to a beneficial low (<4.5) vaginal pH?
- ▶ Does oral probiotic treatment lead to increased ongoing pregnancy rates after IVF, compared with rates among placebo and IVF patients in the same centre?

Randomisation and investigational product

Participants will be randomly assigned (1:1) to either the probiotic treatment or matching placebo treatment. The randomisation will be performed centrally by Winlove Probiotics BV by a subject not involved in the study. Blocked randomisation (blocks of four) will be used to ensure a good balance of participants' characteristics in each group. All study products will be sequentially numbered. Coded study products will be handed over to the researchers to ensure that both investigators and participants will be blind to the assigned arm. When the study has ended, participants will be divided into two blinded groups, which will be used in the statistical analysis. After performing the analyses, code numbers will be opened by the coordinating and principal investigator. Emergency unblinding by the principal investigator is also admitted for single participants who will interrupt the trial because of serious adverse events (SAEs). The active treatment in the present study is a probiotic food supplement. The probiotic treatment is a multispecies probiotic formulation developed by Winlove Probiotics (The

Netherlands) which consists of five specifically selected probiotic *Lactobacilli* strains (proprietary formulation). The probiotic treatment will be provided as powder in sachets, intended for dissolving and subsequent oral use. Participants will consume orally a daily dose of 3 grams, dissolved in a glass of lukewarm water (100 mL), for a period of 8 weeks. A daily dose of the study product contains at least 5×10^9 colony forming units of live probiotic bacteria. The placebo treatment is developed to match the active probiotic treatment and will contain the same consumption instructions. The placebo is indistinguishable in appearance (eg, colour), smell and taste from the probiotic study product, but without active ingredients (eg, probiotic strains). Adherence will be determined by collecting the empty sachets and, if applicable, any remaining study product at the last in-person study visit at week 8.

Sample size

The study will involve a treatment of 8 weeks. During this time frame, the expected spontaneous shift (in the placebo group) from an initial low to a medium/high profile is 54%.²⁷ No pilot data is available on the predicted VMB profile switch following oral probiotics. Based on a number of assumptions, we estimate that in the same time frame of 8 weeks the proportion of patients treated with oral probiotics switching from an initial low to a medium/high profile (effect) will be 80%. The stated difference of improvement between the two treatment arms would be clinically significant and is therefore a justified number for power calculations. With a significance criterion of $\alpha=0.05$, a power=0.80 and a β cut-off of 20%, the minimum sample size needed with this effect size is $n=50$ patients per group. Thus, a total of 100 patients, 50 in the placebo (control) group and 50 in the probiotics (treatment) group, is adequate to test the study hypothesis.

Based on data from the clinical application of the ReceptIVFity test in IVF patients in Europe, we expect the prevalence of VMB low profile among IVF patients to be 30–35%, independently of their IVF cycle.¹⁹ Therefore, around 330 IVF patients are expected to be enrolled in the study and screened, in order to reach the required 50 participants in each of the two groups (100 in total). A 10% drop-out rate has been calculated, leading to a total amount of 110 patients.

Study procedure

The study procedures will be performed at intake, 4, 6 and 8 weeks after start of treatment with probiotics or placebo. Vaginal swabs, rectal swabs and pH sampling will be collected (figure 1). All women will have a follow-up period of 12 months after inclusion in which pregnancy results will be monitored. Patients who decline further participation at any time point and patients experiencing adverse effects that, in the opinion of study investigators, indicate that the study product should be stopped will be discontinued.

- ▶ The bacterial species residing in the vagina will be reported as individual species and using measures of alpha diversity (number and diversity of species in each sample).
- ▶ Differences in pregnancy rate in the intervention and control group will be determined by an independent samples t-test.
- ▶ The association between oral probiotic treatment and a beneficial low vaginal pH will be determined in a 2×2 table, and the McNemar test will be used for paired data.

Multivariate analysis will be performed using logistic regression with a selection of covariates that are known predictors for reproductive/vaginal health; that is, age, duration of infertility, primary versus secondary infertility and body mass index.

Data management

Data will be collected in a Castor EDC database by the subinvestigator, research nurse and trained research assistant. Data handling will be done anonymously. Missing data will be mentioned along with the reason. Data will be preserved for 15 years in compliance with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens). There are no restrictions in data access for trial investigators.

The data that support the findings of this study are available from the corresponding author on reasonable request.

Adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product. The end of the study is defined as 1 month after the last study visit. The follow-up period of 1 year and the questionnaire that will be sent after 1 year are not considered as being part of the study period. (Serious) adverse events ((S)AEs) should be reported for all events during the study and 1 month after the last study visit, but not for the total follow-up period. All adverse events reported spontaneously by the subject or by the investigator or his staff will be recorded. The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events. The sponsor will report the SAEs in accordance with current local and national adverse event reporting policies.

Monitoring

Data monitoring will be performed in compliance with good clinical practice (GCP) and the rules and regulations to achieve high-quality research and ensure the safety of participants. A certified independent party of the MUMC+ will monitor the study according to the monitor plan.

Patient and public involvement

The patients and public were not involved in the planning of this study.

ETHICS AND DISSEMINATION

This study has been approved by the Medical Ethics Committee of the MUMC, registration number METC 22–019, date of approval 25 September 2023. This study is registered at the Dutch trial registry, registration number CCMO NL81210.068.22, registered 25 September 2023.³²

The investigator obtains written informed consent before study participation from all participants (online supplemental file S1. Participant consent form). A trained research nurse will confirm that the participants understand the research and agree to participate voluntarily. Due to the nature of the study, the study team and ethics committee decided that a safety monitoring board is not necessary. All participants will be insured by the sponsor in case of harm due to participation. To ensure confidentiality, all participants will be assigned an ID code after study inclusion, which will be used on all documents and data. The study will be conducted according to the Helsinki Declaration and in accordance with the Medical Research Involving Human Subjects Act (WHO), the Guideline for GCP and other regulatory requirements. All modifications to the protocol, besides minor corrections or insignificant administrative changes, will require formal amendment that has to be approved by the Medical Ethics Committee prior to implementation. Results will be disseminated through peer-reviewed publications and shared with the academic and medical community, patient and funding organisations at international scientific meetings in order to contribute to optimise fertility care.

COLLABORATIVE AGREEMENT BETWEEN PARTIES

ARTPred will participate in the study by performing the VMB testing and covering costs related to sample shipment to the testing facility and samples' testing. ARTPred will also isolate DNA in collected samples, ship part to Winlove which will compare the bacteria with their strains used in the probiotic composition, after which Winlove sends the remaining samples to MUMC+. Winlove will participate in the study by providing the investigational products (probiotic and placebo treatment) and covering the cost of production and shipment of treatments. For any remaining product, Winlove will cover the cost of shipping back the probiotics to its facilities and destroying them. Winlove will also cover the cost of probiotic strain testing in vaginal and rectal swabs by qPCR. Local costs (eg, collecting the swabs, samples storage) will be covered by the fertility clinic at MUMC+. Winlove and ARTPred are not the sponsors of this study.

The fertility clinic at MUMC+, any collaborating clinics, Winlove and ARTPred have agreed to collaborate in the present study by means of a collaboration and confidentiality agreement signed by all parties. Winlove and ARTPred will have the chance to review and provide input to publications based on the generated data. Ultimately though, the decision on whether and how to publish data from the proposed study will be in the hands of the research team from MUMC+/UM.

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