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The 'Pleasure&Pregnancy' web-based interactive educational program versus expectant management in the treatment of unexplained subfertility: the protocol for a randomized controlled trial

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Title

The 'Pleasure&Pregnancy' web-based interactive educational program versus expectant management in the treatment of unexplained subfertility: the protocol for a randomized controlled trial

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Abstract

Introduction: Many subfertile couples are diagnosed with (relatively) unexplained subfertility and a good prognosis. National professional guidelines (e.g. the Netherlands and UK) advise 'expectant management' for 6-12 months, in which no interaction with health care staff is offered. Underpowered studies indicate that face-to-face sex-counseling increases the ongoing pregnancy rates of these couples. In patients with other conditions, web-based interactive educational programs have the same effect on sexual functioning as face-to-face sex counseling. The 'Pleasure&Pregnancy randomized controlled trial (RCT)' will examine in couples with unexplained subfertility and a good prognosis whether a new web-based interactive educational program results in a higher chance of naturally conceiving an ongoing pregnancy within six months as compared to expectant management.

Methods and analysis: A multicenter RCT with cost-effectiveness analysis will include heterosexual couples diagnosed with (relatively) unexplained subfertility and a good prognosis in Dutch and Belgian secondary or tertiary fertility clinics. Couples will be randomized between six months of expectant management and six months of the Pleasure&Pregnancy-program. This new web-based interactive educational program includes eight progressive modules of information (on the biology of conception and pleasurable sex) and sensate focus, couple communication and mindfulness exercises. Couples are offered interaction with their coaches via email and can take part in three moderated chat sessions with peers. The primary outcome of this RCT is the probability of naturally conceiving an ongoing pregnancy within six months after randomization. Secondary outcomes include time-to-pregnancy, live birth rate, costs, sexual functioning and personal and relational wellbeing. Analysis will be according to intention to treat.

Ethics and dissemination: This study has been approved by the Medical Ethical Committees of the Academic Medical Centre (the Netherlands) and the Leuven University Hospital (Belgium). The findings of this RCT will be disseminated through presentations at international scientific meetings and peer-reviewed publications.

Trail registration: NTR5709

Key words

Subfertility; pregnancy; sex-counseling; web-based intervention; natural conception.

Strengths and limitations of the study

- This is an adequately powered multicentre randomised controlled trial (RCT)
- Selection and selective reporting bias has been limited
- The pathway based on which the program is expected to work will be examined
- Acceptance of the hypothesis of this RCT, would have major impact on clinical practice
- Only the statistician is blinded, which can be considered a limitation

Introduction

Subfertility or the inability to conceive after at least one year of unprotected intercourse, affects one in ten heterosexual couples and about half of them will seek medical help.[1] About half of the couples turning to fertility clinics are diagnosed with (relatively) unexplained subfertility as their diagnostic fertility work-up shows tubal patency, an ovulatory cycle and more than 3 million progressive sperm per ejaculate. [2 3] The prognosis of couples with unexplained subfertility is considered 'good' if the validated model of 'Hunault' predicts at least 30% chance of naturally conceiving a live born child within a year after diagnosis. [3]. In these couples, starting with intra-uterine insemination with controlled ovarian stimulation immediately after diagnosis has no added value. [4] Therefore, guidelines of several national professional associations (e.g. the Netherlands, the UK) advise to offer couples with unexplained subfertility and a good prognosis 'Expectant Management' (EM) rather than medically assisted reproduction (MAR) for at least six months in.[3 5 6] None of these guidelines advice to provide couples any interaction with health care staff during EM. [3 5 6]

An underpowered randomized controlled trial (RCT)(n=20) and a case-control study (n=17 cases) suggest that offering face-to-face sex-counseling rather than EM increases the ongoing pregnancy rates of couples with unexplained subfertility (respectively: 35% vs. 11% within 12 months and 60% vs. 11% within 18 months).[7 8] These preliminary findings are plausible as they can be explained by a series of findings from larger scale cohort studies. More specifically, subfertile couples have limited coïtal frequency (on average 7x/month)[9] and coital frequency affects the probability of natural conception. [10] In addition, sex counseling proved to improve the sexual functioning of couples with other conditions (i.e. prostate cancer of men; i.e. low sexual desire of women)[11 12] and the sexual functioning of subfertile men is associated with their coital frequency.[9]

In heterosexual couples confronted with prostate cancer of the man, web-based interactive educational programs proved to have the same effect on sexual functioning as more expensive face-to-face sex counseling.[12] Our group recently developed a 6-months 'Pleasure&Pregnancy'-program, which has yet to be tested.[13] This web-based interactive educational program includes eight progressive modules with sensate focus, couple communication and mindfulness exercises and offers information on the biology of conception and interaction with coaches and peers.

Methods and analysis

This protocol, was based on the SPIRIT-guidelines.[73]

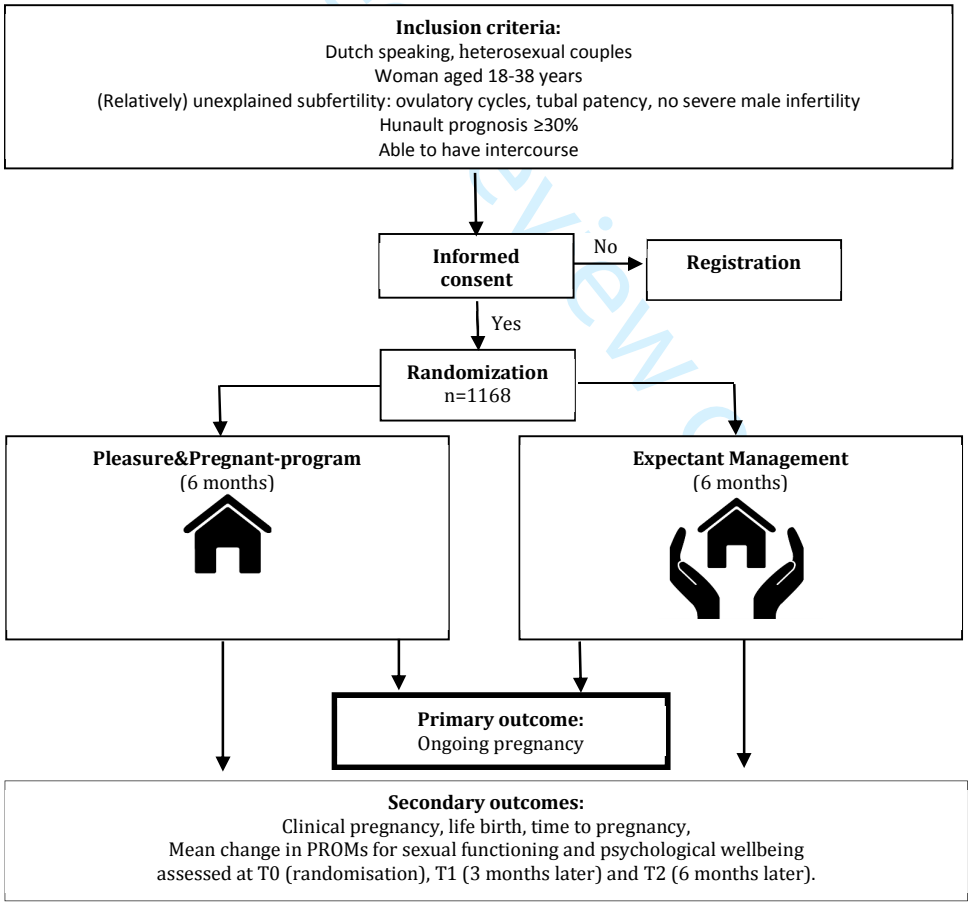
Aim

The 'Pleasure&Pregnancy'-RCT examines in couples with unexplained subfertility and a good prognosis whether a new web-based interactive educational program results in a higher probability of a naturally conceived ongoing pregnancy within six months than standard expectant management.

Design

This is a multicenter RCT with cost-effectiveness analysis (CEA). Couples will be allocated (1:1 allocation ratio) to the two parallel groups of the 'Pleasure&Pregnancy-program' and 'Expectant Management' (EM) and sample size calculations are based on a superiority framework. [14] Only the statistician will be blinded, as the nature of the intervention does not allow blinding couples or recruiters. The flow-chart of this 'Pleasure&Pregnancy-RCT' is presented in figure 1. Recruitment started in June 2016.

Figure 1. Flow-chart of the Pleasure&Pregnancy-RCT



Ethics

This RCT has been approved by the Medical Ethical Committees of the Academic Medical Centre (the Netherlands) and the Leuven University Hospital (Belgium). Before randomization, written informed consent is obtained in patients fulfilling the inclusion criteria.

Setting

This multicenter RCT will be conducted over a 42 months period in secondary or tertiary fertility clinics in The Netherlands and Belgium, which started in June 2016. So far, 28 clinics have included patients and another 19 are in the process of obtaining ethical approval. The regularly updated list of participating clinics can be obtained from the study website. [15] Clinics that want to contribute to the Pleasure&Pregnancy-RCT, can contact any of the authors. The RCT is coordinated and monitored by the Dutch Consortium for Healthcare Evaluation in Obstetrics and Gynecology NVOG Consortium.

Eligible participants

Dutch speaking heterosexual couples, in which the woman is between 18 and 38 years old, who are diagnosed with unexplained subfertility and have a 'Hunault'-prognosis of at least 30% chance of naturally conceiving a live born child within a year after diagnosis. In line with the Guidelines of the Dutch Society of Obstetrics and Gynecology (which allows slight variations in performed diagnostic tests), subfertility is (relatively) unexplained in case of tubal patency, an ovulatory cycle and more than 3 million progressive sperm per ejaculate.[2 3] Tubal patency can be documented by a negative chlamydia anti-body test and/or by a hysterosalpingography, HyCoSY or laparoscopy showing at least one patent tube. Cycles are considered ovulatory if they are regular (i.e. duration of 23-35 days with less than 8 days variation) and if ovulation is demonstrated by a basal body temperature curve, a midluteal serum progesterone concentration or by sonographic cycle monitoring. [4] The Hunault-prognosis is calculated based on female age, percentage of progressive sperm, duration of subfertility, type of subfertility (primary or secondary), and referral status (self-referral, secondary or tertiary care referral). [2 16] Couples in whom the medical history detected somatic or psychological problems interfering with their ability to have intercourse or who are undergoing face-to-face sex-counseling are not eligible for this trial. Other types of counseling or alternative medicine do not affect eligibility.

Sample size

We hypothesize that the Pleasure&Pregnancy-program will increase the chance of conceiving an ongoing pregnancy within six months by increasing pleasurable sex and thereby increasing intercourse frequency and thereby conception rates.

Assuming an ongoing pregnancy rate of 27% in the control group [4] and 35% in the intervention group (i.e. based on a case-control study of sex-counseling)[8] and a 10% drop-out rate (i.e. based on no drop-out in the similar case-control study and on couples' strong wish to conceive) [8], we will need 582 couples in each arm of the study (two-sided test, power of 80%, alpha=0.05).

Attaining this sample size within the 42 months recruitment period of this RCT seems feasible. More specifically, we expect Dutch clinics to diagnose 17,500 eligible couples

during the 42 months recruitment period. Based on the prevalence of subfertility and the size of the Dutch population, we expect the incidence of subfertility to be 20,000 couples per year. [17] The probability of diagnosing unexplained subfertility and a good prognosis is 25%. [18] This means that if one third of the Dutch fertility clinics take part and if 50% of eligible patients are willing to participate, 2,916 couples could be randomized during our 42 months recruitment period while our required sample size is 1,164 couples.

Clinics are likely to take part for the following reasons: (i) physicians prefer taking action while being advised by professional guidelines to delay medically assisted reproduction [19], (ii) the professional association of Dutch gynecologists (NVOG) prioritized the objective of this research project over five other objectives [20]; (iii) participation only requires minimal time investments from the participating clinics as the interactions for the new Pleasure&Pregnancy-program are provided to all patients by the project team (Academic Medical Center, Amsterdam and University Hospital Leuven, Belgium). We expect many couples to take part as couples going through expectant management (i.e. usual care) have been reported to be desperate for support. [21 22]

Recruitment

Eligible couples are informed and both partners are asked for written informed consent by professionals involved in their health care (e.g. clinicians, study nurse). Couples declining participation are registered and their rationales are noted. Participants are informed that they may choose to discontinue the Pleasure&Pregnancy-program once an ongoing pregnancy is diagnosed. Background characteristics of participants are entered in an electronic data base by the recruiters.

Randomization

A central internet-based randomization program, allocates (1:1 allocation ratio) the eligible consenting couples to six months of the Pleasure&Pregnancy-program (i.e. intervention group) or six months of 'Expectant Management' (EM; i.e. control group receiving care as usual) while relying on minimization to ensure a balanced allocation within each clinic. The recruiters cannot access the allocation sequence and only receive the allocation code after having entered the inclusion criteria in the online randomization program.

Interventions

In case of randomization to EM, couples are simply sent home for six months to continue to attempt natural conception without being offered interaction with health care staff as specified for care as usual by the Dutch guideline [http://nvog-documenten.nl/index.php?pagina=/richtlijn/item/pagina.php&richtlijn_id=869].

In case of randomization to the Pleasure&Pregnancy-program, couples are sent home for six months to continue to attempt natural conception while having access to the interactive web-based educational Pleasure&Pregnancy-program. At the time of randomization couples chose a pseudonym (i.e. to guarantee their privacy, also in the group chat sessions) and both partners provide an email address on which to receive a personal access code for the website of the Pleasure&Pregnancy-program. During the Pleasure&Pregnancy-RCT, we use web-based tracking to follow-up couples' adherence to the Pleasure&Pregnancy-program.

The Pleasure&Pregnancy-program was designed based on expert opinion, literature review and patient interviews. [13] The Pleasure&Pregnancy-program includes eight progressive web-based modules of information and exercises which become available one-by-one with 2-weeks intervals and remain available for the rest of the six months' time period. In addition to the modules, a set of frequently asked questions on the biology of conception are answered to prevent behavior potentially negatively impacting ongoing pregnancy rates (e.g. use of lubricants compromises sperm quality).[23] Finally, couples can email the team of coaches (i.e. a midwife-researcher, sexologist, gynecologist and a biologist of the Academic Medical Centre Amsterdam and the University Hospital of Leuven) and can take part in three facilitated group chat sessions with other anonymized patients. Regarding the modules, the information and exercises aim to increase pleasurable sexual sensations and responses and thereby intercourse frequency and ongoing pregnancy rates. More specifically, couples are informed on correct and misconceptions about how to increase and maintain pleasurable sex. Each module includes three different types of (couple or individual) exercises. Sensate focus exercises teach couples to focus on their own and their partner's pleasurable sexual sensations and responses.[24-26] Mindfulness exercises help couples to decrease cognitive distraction during sexual activity and to decrease performance anxiety and muscles tension. [27 28] Couple communication exercises encourage couples to discuss issues interfering with relational and/or sexual functioning. [26 29]

Outcome measures

The same outcomes are followed up in both arms of the Pleasure&Pregnancy-RCT. In non-pregnant couples data are collected from randomization until eight months later (i.e. maximal two months to fill out the questionnaires disseminated six months after randomization). In pregnant couples data are collected until birth or pregnancy termination.

The primary outcome of this Pleasure&Pregnancy-RCT is the probability of a naturally conceived andongoing pregnancy (defined as a viable intrauterine pregnancy of at least 12 weeks duration confirmed by an ultrasound scan)[30] within six months after randomization. Allied secondary outcomes assessed in couples achieving the primary outcome are the live birth rate and the time to pregnancy. Costs are also be assessed. Finally, the sexual functioning and personal and relational wellbeing of both partners of participating couples is assessed online after sending an email link to a package of patient reported outcome measures (PROMs) at randomization and 3- and 6-months later. The packages of PROMs include five questionnaires, addressing sexual functioning (n=1; different questionnaire for men and women), personal wellbeing (n=3) and relational wellbeing (n=1). The following characteristics of the PROMs are outlined in table 1: outcome, name, source of the used version, number of questions, subscales (minimal and maximal scores and interpretation), reliability measures and demonstrated type of validity. Non-respondents are send two email reminders and are telephoned by the study nurses of their hospital if needed. In addition, participants are asked to register the following in an online event log calendar: their menstrual period (only women) and when they had coitus and how they experienced it (with the PROM 'QSE' outlined in table 1; women and men).

Table 1. Characteristics of the Patient Reported Outcome Measures

Dimen-sions	Outcome	Name of questionnaire (abbreviation)	Source for the used version of the questionnaire	Nr of ques-tions	(Sub)scales (min-max scores) [Interpretation]	Reliability measures	Demonstrated types of validity
Sexual functioning	Sexual pleasure	Quality of Sexual Experience (QSE)	Dutch: Reciprocally translated by Prof Dr E Laan, University of Amsterdam English similar version [51]	8	Total (8-56) [The higher, the better]	TRR[3] total score: *r* =.76 TRR per question: *r*=0.63-0.75 ITC: α range =.71-.88 IC per question: α=0.71-0.88 [52]****	Known-group validity, convergent validity [52]****
	Sexual functioning of women	Female Sexual Function Index (FSFI)	Dutch [53] English similar version [54]	19	Total score (2.0-36.0) and 6 subscales: sexual interest/ desire (1.2-6.0), sexual arousal (0.0-6.0), lubrication (0.0-6.0), orgasm (0.0-6.0), sexual satisfaction (0.8-6.0), pain (0.0-6.0) [The higher, the better]	IC per subscale: α=0.87-0.98 IC total: α=0.97 TRR per subscale: r =0.71-0.97 TRR total score: r =0.93 ITC per subscale: 0.59-0.95 ITC total: 34-95 [55]**	Construct validity, Discriminant validity, Divergent validity [55]**
	Sexual function-ing of men	International Index of Erectile Function (IIEF)	Dutch [56] English similar version [57]	15	Total score (5-75) and 5 subscales: erectile function (1-30), orgasm (0-10), sexual desire (2-10), sexual satisfaction (0-15), overall satisfaction (2-10) [The higher, the better]	IC per domain: α= 0.73-0.99 IC total: α >.90 TRR total: r =0.82 TRR per item: r =0.64-0.84 ITC per domain: r =0.30-0.76 [58]****	Construct validity, Discriminant validity, Convergent validity, Divergent validity [58]****
Personal wellbeing	Overall quality of life (General health)	EuroQol 5D scale (EQ-5D)	Dutch [59] English similar version [60]	6	Total VAS (0-100) and 5 subscales: mobility (1-3), self-care (1-3), daily activities (1-3), pain (1-3), mood (1-3) [For total VAS: the higher, the better. For subscales: the lower, the better]	IC of the five domains: α=0.85 [61]**** ICC[4]=.78 [62]	Convergent validity, discriminative validity [61]**** Criterion, concurrent, construct validity [63]****
	Fertility quality of life	The fertility quality of life (FertiQol; Core FertiQol without treatment module)	Dutch [64] English similar version [65]	24	Total (0-96) and 4 subscales: emotional (0-24), relational (0-24), mind/body (0-24), social (0-24) [The higher, the better]	IC per subscale: α =0.72-0.91 ITC per domain: r = (-0.29)-(-0.71) [66]*	Convergent validity [66]*
	Anxiety and depression	Hospital Anxiety and Depression Scale (HADS)	Dutch [67] English similar version [68]	14	Total (0-42) and 2 subscales: anxiety (0-21), depression (0-21) [The lower, the better]	IC for total: α >0.82 IC per subscale: α =0.71-0.86 TRR per subscale: *r* =0.86-0.89 TRR for total: r =0.91 [69]** IC per subscale: α =0.75-0.87 ITC per subscale: 0.22-0.55 [70]***	Concurrent validity [69]** Convergent validity [70]***
Rela-tional wellbe	Relation-ship satis-faction	Revised Dyadic Adjustment Scale (R-DAS)	Dutch: Reciprocally translated by Prof Dr E Laan, University of Amsterdam. English similar version [71]	14	Total score (0-69) and 3 subscales: Dyadic consensus (0-30), dyadic satisfaction (0-20), dyadic cohesion (0-19) [The lower, the better]	IC per subscale: α=0.80-0.85 IC total score: α=0.90 TRR per subscale: r =0.80-.89 TRR total score: r =0.95 [72]****	Construct validity Criterion validity [72]****

Abbreviations used in this table: ITC=Item Total Correlation; IC=Internal Consistency; TRR=Test-retest reliability.
*Study using the same Dutch version of the questionnaire in subfertile patients
**Study using the same Dutch version of the questionnaire but not in subfertile patients
***Study using the most similar version of the questionnaire in another language in subfertile patients
****Study using the most similar version of the questionnaire in another language but not in subfertile patients

Analysis

The web-based data will all by entered and analyzed in the Statistical Package for Social Sciences (SPSS, version 22.0). No interim analysis have been planned and no adverse events are expected due to the nature of the educational intervention. Analysis will be according to intention to treat and p-values

≤0. 05 will be considered to indicate statistically significant differences. To examine whether the randomization resulted in two balanced groups the following six assessed background characteristics, intercourse frequency and all baseline PROMs will be compared between the intervention and control group: female age, type of infertility (primary/secondary), duration of infertility, intoxications (e.g. smoking), body mass index and total motility sperm count.

Differences in ongoing pregnancy rate will be expressed as relative risks. Kaplan-Meier survival curves for each treatment group will assess time to ongoing pregnancy. PROMs will be processed according to their manuals. Linear mixed models will be used to evaluate treatment, time and interactive effects on all outcomes. Regarding PROMs assessed in both partners separately, the factor gender (modelled as fixed effect) and clustering within couples (modelled as random intercepts) will be taken into account. This means that the effect of pregnancy on the quality of life (i.e. VAS EQ-5D scores) will be evaluated with linear mixed models. In case of an interaction between pregnancy and treatment the difference in quality of life between both groups will be assessed in the women who did not become pregnant.

Economical Evaluation

We will conduct a cost-effectiveness analysis (CEA) with a time horizon of six months after randomization from the perspectives of the health care payer perspective (capturing direct costs).

The costs per ongoing pregnancy in both arms of the RCT (Pleasure&Pregnancy-program or expectant management) will be calculated and compared using a decision model taking costs, ongoing pregnancies and change in Quality-adjusted life years (QALYs) into account. The change in QALYs will be based on the responses to the EQ-5D-questionnaire at randomization and six months later. Regarding the costs, actually used resource volumes of the Pleasure&Pregnancy-program will be recorded and attached to standardized unit costs (i.e. calculated based on actual expenses made by the centralized location of the Academic Medical Center). In addition, we will conduct a Budget Impact analysis (BIA) from the health care payer perspective (capturing direct health care costs for Dutch health insurance) and from the societal perspective (additionally capturing indirect health care costs due to productivity of patients). The time horizon of this BIA will be three years to include costs of, amongst others: Medically Assisted Reproduction for the couples who did not conceive during the RCT, miscarriage, pregnancy and delivery of singletons and twins, NICU admission and extra care in the first year of the live of a new born baby. For this BIA, we will evaluate three scenarios depending on the implementation rate of the Pleasure&Pregnancy-program, namely 100%, 85% and 70% of Dutch couples.

Ethics and dissemination

The Institutional Review Board (IRB) of the Academic Medical Center Amsterdam (the Netherlands) approved the Pleasure&Pregnancy-RCT (IRB registration number: 2015_317). If important protocol modifications would have to be made, the IRB, recruiters and trial registry will be notified. This trial has been registered in the Netherlands trial register (NTR5709). The findings of this RCT will be disseminated through presentations at international scientific meetings and peer-reviewed publications. We do not intend to collaborate with a medical writer.

Discussion

This protocol outlines our efforts to limit the risk of bias in our RCT. We limited the risk of selection bias in the Pleasure&Pregnancy-RCT with computerized randomization, allowing random sequence generation. In addition, we will check whether randomization was successful in equally dividing baseline demographic, medical, sexual and psychosocial confounders between groups. Including sexual confounders (i.e. sexual functioning, pleasure and coital frequency) is relevant as they are central to the pathway based on which we expect the program to work. Including psychosocial confounders is relevant as the effect of psychosocial interventions on pregnancy rates is uncertain.[31-35] We limited the risk of detection and ascertainment bias by blinding the statistician. We cannot blind participants and recruiters as the intervention group receives an additional psychosocial intervention, while the control group will simply be send home without receiving a placebo intervention. Finally, publishing this protocol, which specifies all outcomes, will prevent selective reporting bias. All outcomes of the Pleasure&Pregnancy-RCT will be assessed reliably. More specifically, ongoing clinical pregnancies are confirmed by ultrasound diagnosis and all included PROMs are assessed with valid and reliable questionnaires. Other strengths of the Pleasure&Pregnancy-RCT are the power calculation, intention-to treat analysis and the standardized format of the intervention.

The Pleasure&Pregnancy-program is a comprehensive educational program[31], which includes information, couple communication, sensate focus and mindfulness exercises and interaction. The Pleasure&Pregnancy-RCT will primarily test the hypothesis that this program increases ongoing pregnancy rates when compared to EM. If it is effective, it will be interesting to find out which of its elements contribute to this effect via which pathway. We expect the Pleasure&Pregnancy-program to work by increasing pleasurable sex, which increases coital frequency, which in turn increases ongoing pregnancy rates. It is, however, also biologically plausible that improved sexual arousal and pleasure have a direct positive effect on ongoing pregnancy rates. More specifically, in men, orgasms following higher levels of sexual arousal have been associated with better sperm quality.[36] In women, orgasms may enhance passive and active sperm transport. [37,38] Female sexual arousal also enhances lubrication of the vagina, neutralizes pH and increases perivaginal vasocongestion, which in turn improves mobility and survival of spermatozoa.[39,40] Vaginal dryness is associated with the use of commercial lubricants, of which some compromise sperm quality. [23, 41]

If this RCT proves that the Pleasure&Pregnancy-program is effective, we will advise to offer an interactive educational program as first line treatment in couples with unexplained subfertility before embarking on medically assisted reproduction. As more couples would be

conceiving naturally, the Pleasure&Pregnancy-program would decrease the 67% of couples returning for MAR after having continued to attempt natural conception for six months. [42] This would be highly relevant as MAR is associated with many drawbacks including significant costs, treatment burden and increased probability of multiple pregnancy, obstetric and perinatal complications, congenital abnormalities and long-term health risks for offspring. [43-50] If the Pleasure&Pregnancy-program increases the number of couples conceiving naturally and/or improves sexual functioning, it would be worthwhile to consider also offering it to couples with other infertility diagnoses at other treatment stages, or even to couples who are interested to improve their sexual functioning. The mHealth format of the Pleasure&Pregnancy-program will facilitate its low-cost wide-spread implementation.

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Authors' contribution

EAFD, IC, TMD, CL, SR and MW designed the trial, developed the protocol and applied for funding. EAFD, IC and FD applied for ethical approval and implemented the logistics of the trial. All authors read, revised and approved the final manuscript.

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Competing interests

The authors declare to have no financial or non-financial conflicts of interest.

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Other declarations

The following other declarations are not applicable to this manuscript: consent for publication, availability of data and material and endnotes.

List of abbreviations

BIA: budget impact analysis; CEA: cost-effectiveness analysis; MAR: medically assisted reproduction; PROMS: Patient reported outcome measures; RCT: randomized controlled trial.

Availability of data and material

Not applicable.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32 Dupl	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33X	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The 'Pleasure&Pregnancy' web-based interactive educational program versus expectant management in the treatment of unexplained subfertility: the protocol for a randomized controlled trial

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Title

The 'Pleasure&Pregnancy' web-based interactive educational program versus expectant management in the treatment of unexplained subfertility: the protocol for a randomized controlled trial

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Abstract

Introduction: Many subfertile couples are diagnosed with (relatively) unexplained subfertility and a good prognosis. National professional guidelines (e.g. the Netherlands and UK) advise 'expectant management' for 6-12 months, in which no interaction with health care staff is offered. Underpowered studies indicate that face-to-face sex-counseling increases the ongoing pregnancy rates of these couples. In patients with other conditions, web-based interactive educational programs have the same effect on sexual functioning as face-to-face sex counseling. The 'Pleasure&Pregnancy randomized controlled trial (RCT)' will examine in couples with unexplained subfertility and a good prognosis whether a new web-based interactive educational program results in a higher chance of naturally conceiving an ongoing pregnancy within six months as compared to expectant management.

Methods and analysis: A multicenter RCT with cost-effectiveness analysis will include heterosexual couples diagnosed with (relatively) unexplained subfertility and a good prognosis in Dutch and Belgian secondary or tertiary fertility clinics. Couples will be randomized between six months of expectant management and six months of the Pleasure&Pregnancy-program. This new web-based interactive educational program includes eight progressive modules of information (on the biology of conception and pleasurable sex) and sensate focus, couple communication and mindfulness exercises. Couples are offered interaction with their coaches via email and can take part in three moderated chat sessions with peers. The primary outcome of this RCT is the probability of naturally conceiving an ongoing pregnancy within six months after randomization. Secondary outcomes include time-to-pregnancy, live birth rate, costs, sexual functioning and personal and relational wellbeing. Analysis will be according to intention to treat.

Ethics and dissemination: This study has been approved by the Medical Ethical Committees of the Academic Medical Centre (the Netherlands) and the Leuven University Hospital (Belgium). The findings of this RCT will be disseminated through presentations at international scientific meetings and peer-reviewed publications.

Trail registration: NTR5709

Key words

Subfertility; pregnancy; sex-counseling; web-based intervention; natural conception.

Strengths and limitations of the study

- This is an adequately powered multicentre randomised controlled trial (RCT)
- Selection and selective reporting bias has been limited
- The pathway based on which the program is expected to work will be examined
- Acceptance of the hypothesis of this RCT, would have major impact on clinical practice
- Only the statistician is blinded, which can be considered a limitation

Introduction

Subfertility or the inability to conceive after at least one year of unprotected intercourse, affects one in ten heterosexual couples and about half of them will seek medical help.[1] About half of the couples turning to fertility clinics are diagnosed with (relatively) unexplained subfertility as their diagnostic fertility work-up shows tubal patency, an ovulatory cycle and more than 3 million progressive sperm per ejaculate. [2 3] The prognosis of couples with unexplained subfertility is considered 'good' if the validated model of 'Hunault' predicts at least 30% chance of naturally conceiving a live born child within a year after diagnosis. [3] In these couples, starting with intra-uterine insemination with controlled ovarian stimulation immediately after diagnosis has no added value. [4] Therefore, guidelines of several national professional associations (e.g. the Netherlands, the UK) advise to offer couples with unexplained subfertility and a good prognosis 'Expectant Management' (EM) rather than medically assisted reproduction (MAR) for at least six months in.[3 5 6] None of these guidelines advice to provide couples any interaction with health care staff during EM. [3 5 6]
An underpowered randomized controlled trial (RCT)(n=20) and a case-control study (n=17 cases) suggest that offering face-to-face sex-counseling rather than EM increases the ongoing pregnancy rates of couples with unexplained subfertility (respectively: 35% vs. 11% within 12 months and 60% vs. 11% within 18 months).[7 8] These preliminary findings are plausible as they can be explained by a series of findings from larger scale cohort studies. More specifically, subfertile couples have limited coïtal frequency (on average 7x/month)[9] and coital frequency affects the probability of natural conception. [10] In addition, sex counseling proved to improve the sexual functioning of couples with other conditions (i.e. prostate cancer of men; i.e. low sexual desire of women)[11 12] and the sexual functioning of subfertile men is associated with their coital frequency.[9]

In heterosexual couples confronted with prostate cancer of the man, web-based interactive educational programs proved to have the same effect on sexual functioning as more expensive face-to-face sex counseling.[12] Our group recently developed a 6-months 'Pleasure&Pregnancy'-program, which has yet to be tested (Dreischor et al, 2019 The development of the Pleasure&Pregnancy-program. In preparation)
This web-based interactive educational program includes eight progressive modules with sensate focus, couple communication and mindfulness exercises and offers information on the biology of conception and interaction with coaches and peers.

Methods and analysis

This protocol, was based on the SPIRIT-guidelines.[13]

Aim

The 'Pleasure&Pregnancy'-RCT examines in couples with unexplained subfertility and a good prognosis whether a new web-based interactive educational program results in a higher probability of a naturally conceived ongoing pregnancy within six months than standard expectant management.

Design

This is a multicenter RCT with cost-effectiveness analysis (CEA). Couples will be allocated (1:1 allocation ratio; computerized randomization) to the two parallel groups of the 'Pleasure&Pregnancy-program' and 'Expectant Management' (EM) and sample size calculations are based on a superiority framework. [14] Only the statistician will be blinded, as the nature of the intervention does not allow blinding couples or recruiters. The flow-chart of this 'Pleasure&Pregnancy-RCT' is presented in figure 1. Recruitment started in June 2016.

Ethics

This RCT has been approved by the Medical Ethical Committees of the Academic Medical Centre (the Netherlands) and the Leuven University Hospital (Belgium). Before randomization, written informed consent is obtained in patients fulfilling the inclusion criteria.

Setting

This multicenter RCT will be conducted over a 42 months period in secondary or tertiary fertility clinics in The Netherlands and Belgium, which started in June 2016. So far, 38 clinics have included patients and another 2 are in the process of obtaining ethical approval. The regularly updated list of participating clinics can be obtained from the study website. [15] Clinics that want to contribute to the Pleasure&Pregnancy-RCT, can contact any of the authors. The RCT is coordinated and monitored by the Dutch Consortium for Healthcare Evaluation in Obstetrics and Gynecology NVOG Consortium.

Inclusion criteria

Dutch speaking heterosexual couples, in which the woman is between 18 and 38 years old, who are diagnosed with (relatively) unexplained subfertility and have a 'Hunault'-prognosis of at least 30% chance of naturally conceiving a live born child within a year after diagnosis are eligible. In line with the Guidelines of the Dutch Society of Obstetrics and Gynecology (which allows slight variations in performed diagnostic tests), subfertility is (relatively) unexplained in case of tubal patency, an ovulatory cycle and more than 3 million progressive sperm per ejaculate.[2 3] Tubal patency can be documented by a negative chlamydia anti-body test [4] and/or by a hysterosalpingography, HyCoSY or laparoscopy showing at least one patent tube. Cycles are considered ovulatory if they are regular (i.e. duration of 23-35 days with less than 8 days variation) and if ovulation is demonstrated by a basal body temperature curve, a midluteal serum progesterone concentration or by sonographic cycle monitoring. [4] The Hunault-prognosis is calculated based on female age, percentage of progressive sperm, duration of

subfertility, type of subfertility (primary or secondary), and referral status (self-referral, secondary or tertiary care referral). [2 16]

Exclusion criteria

Couples in whom the medical history detected somatic or psychological problems interfering with their ability to have intercourse or who are undergoing face-to-face sex-counseling are not eligible for this trial. Other types of counseling or alternative medicine do not affect eligibility.

Sample size

We hypothesize that the Pleasure&Pregnancy-program will increase the chance of conceiving an ongoing pregnancy within six months by increasing pleasurable sex and thereby increasing intercourse frequency and thereby conception rates.

Assuming an ongoing pregnancy rate of 27% in the control group [4] and 35% in the intervention group (i.e. based on a case-control study of sex-counseling)[8] and a 10% drop-out rate (i.e. based on no drop-out in the similar case-control study and on couples' strong wish to conceive) [8], we need 582 couples in each arm of the study or 1164 couples in total (two-sided test, power of 80%, alpha=0.05).

Attaining this sample size within the 42 months recruitment period of this RCT seems feasible. More specifically, we expect Dutch clinics to diagnose 17,500 eligible couples during the 42 months recruitment period. Based on the prevalence of subfertility and the size of the Dutch population, we expect the incidence of subfertility to be 20,000 couples per year. [17] The probability of diagnosing unexplained subfertility and a good prognosis is 25%. [18] This means that if one third of the Dutch fertility clinics take part and if 50% of eligible patients are willing to participate, 2,916 couples could be randomized during our 42 months recruitment period while our required sample size is 1,164 couples.

Clinics are likely to take part for the following reasons: (i) physicians prefer taking action while being advised by professional guidelines to delay medically assisted reproduction[19], (ii) the professional association of Dutch gynecologists (NVOG) prioritized the objective of this research project over five other objectives [20]; (iii) participation only requires minimal time investments from the participating clinics as the interactions for the new Pleasure&Pregnancy-program are provided to all patients by the project team (Academic Medical Center, Amsterdam and University Hospital Leuven, Belgium). We expect many couples to take part as couples going through expectant management (i.e. usual care) have been reported to be desperate for support. [21 22]

Recruitment

Eligible couples are informed and both partners are asked for written informed consent by professionals involved in their health care (e.g. clinicians, study nurse). Couples declining participation are registered and their rationales are noted. Participants are informed that they may choose to discontinue the Pleasure&Pregnancy-program once an ongoing pregnancy is diagnosed. Background characteristics of participants are entered in an electronic data base by the recruiters.

Randomization

A central internet-based randomization program, allocates (1:1 allocation ratio) the eligible consenting couples to six months of the Pleasure&Pregnancy-program (i.e. intervention group) or six months of 'Expectant Management' (EM; i.e. control group receiving care as usual) while relying on minimization to ensure a balanced allocation within each clinic. The recruiters cannot access the allocation sequence and only receive the allocation code after having entered the inclusion criteria in the online randomization program.

Interventions

In case of randomization to EM, couples are simply sent home for six months to continue to attempt natural conception without being offered interaction with health care staff as specified for care as usual by the Dutch guideline [http://nvog-documenten.nl/index.php?pagina=/richtlijn/item/pagina.php&richtlijn_id=869].

In case of randomization to the Pleasure&Pregnancy-program, couples are sent home for six months to continue to attempt natural conception while having access to the interactive web-based educational Pleasure&Pregnancy-program. At the time of randomization couples chose a pseudonym (i.e. to guarantee their privacy, also in the group chat sessions) and both partners provide an email address on which to receive a personal access code for the website of the Pleasure&Pregnancy-program. During the Pleasure&Pregnancy-RCT, we use web-based tracking to follow-up couples' adherence to the Pleasure&Pregnancy-program.

The Pleasure&Pregnancy-program was designed based on expert opinion, literature review and patient interviews (Dreischor et al. 2019 The development of the Pleasure&Pregnancy-program. In preparation). The Pleasure&Pregnancy-program includes eight progressive web-based modules of information and exercises which become available one-by-one with 2-weeks intervals during the first 3.5 months and remain available for the rest of the six months' time period. In addition to the modules, a set of frequently asked questions on the biology of conception are answered to prevent behavior potentially negatively impacting ongoing pregnancy rates (e.g. use of lubricants compromises sperm quality).[23] Finally, couples can email the team of coaches (i.e. a midwife-researcher, sexologist, gynecologist and a biologist of the Academic Medical Centre Amsterdam and the University Hospital of Leuven) and can take part in three facilitated group chat sessions with other anonymized patients. Regarding the modules, the information and exercises aim to increase pleasurable sexual sensations and responses and thereby intercourse frequency and ongoing pregnancy rates. More specifically, couples are informed on correct and misconceptions about how to increase and maintain pleasurable sex. Each module includes three different types of (couple or individual) exercises. Sensate focus exercises teach couples to focus on their own and their partner's pleasurable sexual sensations and responses.[24-26] Mindfulness exercises help couples to decrease cognitive distraction during sexual activity and to decrease performance anxiety and muscles tension. [27 28] Couple communication exercises encourage couples to discuss issues interfering with relational and/or sexual functioning. [26 29]

Outcome measures

The primary outcome of this Pleasure&Pregnancy-RCT is the probability of a naturally conceiving an ongoing pregnancy (defined as a viable intrauterine pregnancy of at least 12 weeks duration confirmed by an ultrasound scan) [30] within six months after randomization. Allied secondary outcomes assessed in couples achieving the primary outcome are the live

birth rate and the time to pregnancy. Costs are also assessed. Finally, the sexual functioning and personal and relational wellbeing of both partners of participating couples is assessed online after sending an email link to a package of patient reported outcome measures (PROMs) at randomization and 3- and 6-months later. The packages of PROMs include five questionnaires, addressing sexual functioning (n=1; different questionnaire for men and women), personal wellbeing (n=3) and relational wellbeing (n=1). The following characteristics of the PROMs are outlined in table 1: outcome, name, source of the used version, number of questions, subscales (minimal and maximal scores and interpretation), reliability measures and demonstrated type of validity. Non-respondents are send two email reminders and are telephoned by the study nurses of their hospital if needed. In addition, participants are asked to register the following in an online event log calendar: their menstrual period (only women) and when they had coitus and how they experienced it (with the PROM 'QSE' outlined in table 1; women and men).

The same outcomes are followed up in both arms of the Pleasure&Pregnancy-RCT. The follow-up period does, however, differ between non-pregnant and pregnant couples. Non-pregnant couples are followed up from randomization until six months later, unless two months need to be added to remind couples of filling out the last package of PROMs. In pregnant couples data are collected until birth or pregnancy termination.

Table 1. Characteristics of the Patient Reported Outcome Measures

Dimen-sions	Outcome	Name of questionnaire (abbreviation)	Source for the used version of the questionnaire	Nr of ques-tions	(Sub)scales (min-max scores) [Interpretation]	Reliability measures	Demonstrated types of validity
Sexual functioning	Sexual pleasure	Quality of Sexual Experience (QSE)	Dutch: Reciprocally translated by Prof Dr E Laan, University of Amsterdam English similar version [31]	8	Total (8-56) [The higher, the better]	TRR[3] total score: *r* =.76 TRR per question: *r*=0.63-0.75 ITC: α range =.71-.88 IC per question: α=0.71-0.88 [32]****	Known-group validity, convergent validity [32]****
	Sexual functioning of women	Female Sexual Function Index (FSFI)	Dutch [33] English similar version [34]	19	Total score (2.0-36.0) and 6 subscales: sexual interest/ desire (1.2-6.0), sexual arousal (0.0-6.0), lubrication (0.0-6.0), orgasm (0.0-6.0), sexual satisfaction (0.8-6.0), pain (0.0-6.0) [The higher, the better]	IC per subscale: α=0.87-0.98 IC total: α=0.97 TRR per subscale: r =0.71-0.97 TRR total score: r =0.93 ITC per subscale: 0.59-0.95 ITC total: 34-95 [35]**	Construct validity, Discriminant validity, Divergent validity [35]**
	Sexual function-ing of men	International Index of Erectile Function (IIEF)	Dutch [36] English similar version [37]	15	Total score (5-75) and 5 subscales: erectile function (1-30), orgasm (0-10), sexual desire (2-10), sexual satisfaction (0-15), overall satisfaction (2-10) [The higher, the better]	IC per domain: α= 0.73-0.99 IC total: α >.90 TRR total: r =0.82 TRR per item: r =0.64-0.84 ITC per domain: r =0.30-0.76 [38]****	Construct validity, Discriminant validity, Convergent validity, Divergent validity [38]****
Personal wellbeing	Overall quality of life (General health)	EuroQol 5D scale (EQ-5D)	Dutch [39] English similar version [40]	6	Total VAS (0-100) and 5 subscales: mobility (1-3), self-care (1-3), daily activities (1-3), pain (1-3), mood (1-3) [For total VAS: the higher, the better. For subscales: the lower, the better]	IC of the five domains: α=0.85 [41]**** ICC[4]=.78 [42]	Convergent validity, discriminative validity [41]**** Criterion, concurrent, construct validity [43]****
	Fertility quality of life	The fertility quality of life (FertiQol; Core FertiQol without treatment module)	Dutch [44] English similar version [45]	24	Total (0-96) and 4 subscales: emotional (0-24), relational (0-24), mind/body (0-24), social (0-24) [The higher, the better]	IC per subscale: α =0.72-0.91 ITC per domain: r = (-0.29)-(-0.71) [46]*	Convergent validit [46]*
	Anxiety and depression	Hospital Anxiety and Depression Scale (HADS)	Dutch [47] English similar version [48]	14	Total (0-42) and 2 subscales: anxiety (0-21), depression (0-21) [The lower, the better]	IC for total: α >0.82 IC per subscale: α =0.71-0.86 TRR per subscale: *r* =0.86-0.89 TRR for total: r =0.91 [49]** IC per subscale: α =0.75-0.87 ITC per subscale: 0.22-0.55 [50]***	Concurrent validity [49]** Convergent validity [50]***
Relational wellbe.	Relation-ship satis-faction	Revised Dyadic Adjustment Scale (R-DAS)	Dutch: Reciprocally translated by Prof Dr E Laan, University of Amsterdam. English similar version [51]	14	Total score (0-69) and 3 subscales: Dyadic consensus (0-30), dyadic satisfaction (0-20), dyadic cohesion (0-19) [The lower, the better]	IC per subscale: α=0.80-0.85 IC total score: α=0.90 TRR per subscale: r =0.80-.89 TRR total score: r =0.95 [52]****	Construct validity Criterion validity [52]****

Abbreviations used in this table: ITC=Item Total Correlation; IC=Internal Consistency; TRR=Test-retest reliability.
*Study using the same Dutch version of the questionnaire in subfertile patients
**Study using the same Dutch version of the questionnaire but not in subfertile patients
***Study using the most similar version of the questionnaire in another language in subfertile patients
****Study using the most similar version of the questionnaire in another language but not in subfertile patients

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Analysis

The web-based data will all by entered and analyzed in the Statistical Package for Social Sciences (SPSS, version 22.0). No interim analysis have been planned and no adverse events are expected due to the nature of the educational intervention. Analysis will be according to intention to treat and p-values

≤0. 05 will be considered to indicate statistically significant differences. To examine whether the randomization resulted in two balanced groups the following six assessed background characteristics, intercourse frequency and all baseline PROMs will be compared between the intervention and control group: female age, type of infertility (primary/secondary), duration of infertility, intoxications (e.g. smoking), body mass index, total motility sperm count and the diagnostic test to verify tubal patency.

Differences in ongoing pregnancy rate will be expressed as relative risks. Kaplan-Meier survival curves for each treatment group will assess time to ongoing pregnancy. PROMs will be processed according to their manuals. Linear mixed models will be used to evaluate treatment, time and interactive effects on all outcomes. Regarding PROMs assessed in both partners separately, the factor gender (modelled as fixed effect) and clustering within couples (modelled as random intercepts) will be taken into account. This means that the effect of pregnancy on the quality of life (i.e. VAS EQ-5D scores) will be evaluated with linear mixed models. In case of an interaction between pregnancy and treatment the difference in quality of life between both groups will be assessed in the women who did not become pregnant.

Economical Evaluation

We will conduct a cost-effectiveness analysis (CEA) with a time horizon of six months after randomization from the perspectives of the health care payer perspective (capturing direct costs).

The costs per ongoing pregnancy in both arms of the RCT (Pleasure&Pregnancy-program or expectant management) will be calculated and compared using a decision model taking costs, ongoing pregnancies and change in Quality-adjusted life years (QALYs) into account. The change in QALYs will be based on the responses to the EQ-5D-questionnaire at randomization and six months later. Regarding the costs, actually used resource volumes of the Pleasure&Pregnancy-program (i.e. moderated chats and email interaction with professionals) will be recorded and attached to standardized unit costs (i.e. calculated based on actual expenses made by the centralized location of the Academic Medical Center). In addition, we will conduct a Budget Impact analysis (BIA) from the health care payer perspective (capturing direct health care costs for Dutch health insurance) and from the societal perspective (additionally capturing indirect health care costs due to productivity of patients). The time horizon of this BIA will be three years to include costs of, amongst others: Medically Assisted Reproduction for the couples who did not conceive during the RCT, miscarriage, pregnancy and delivery of singletons and twins, NICU admission and extra care in the first year of the live of a new born baby. For this BIA, we will evaluate three scenarios depending on the implementation rate of the Pleasure&Pregnancy-program, namely 100%, 85% and 70% of Dutch couples.

Patient and Public Involvement

The Dutch patient association Freya and the Dutch Society for Obstetrics and Gynaecology (NVOG) confirmed their support for this Pleasure&Pregnancy RCT to the funder. This is not surprising as we started the Pleasure&Pregnancy-program and RCT based on Dutch patients

and gynaecologists sharing that the non-interactive, passive nature of expectant management was a barrier for implementing expectant management. [21 22] Patients were consulted during the development of the Pleasure&Pregnancy program (Dreischor et al. 2019 The development of the Pleasure&Pregnancy-program. In preparation), but not during the design, recruitment and conduct of the Pleasure&Pregnancy RCT. Study participants will be informed on the results of this RCT via the study website. [15] We thank the patients who contributed to the development of the Pleasure&pregnancy program and the patient representatives, who encouraged the funder to fund the Pleasure&Pregnancy RCT.

Ethics and dissemination

The Institutional Review Board (IRB) of the Academic Medical Center Amsterdam (the Netherlands) and the Medical Ethical Committee of the Leuven University Hospital (Belgium) approved the Pleasure&Pregnancy-RCT (IRB registration numbers: 2015_317; s59666). If important protocol modifications would have to be made, the IRB, recruiters and trial registry will be notified. This trial has been registered in the Netherlands trial register (NTR5709). The findings of this RCT will be disseminated through presentations at international scientific meetings and peer-reviewed publications. We do not intend to collaborate with a medical writer.

Discussion

This protocol outlines our efforts to limit the risk of bias in our RCT. We limited the risk of selection bias in the Pleasure&Pregnancy-RCT with computerized randomization, allowing random sequence generation. In addition, we will check whether randomization was successful in equally dividing baseline demographic, medical, sexual and psychosocial confounders between groups. Including sexual confounders (i.e. sexual functioning, pleasure and coital frequency) is relevant as they are central to the pathway based on which we expect the program to work. Including psychosocial confounders is relevant as the effect of psychosocial interventions on pregnancy rates is uncertain.[53-57] We limited the risk of detection and ascertainment bias by blinding the statistician. We cannot blind participants and recruiters as the intervention group receives an additional psychosocial intervention, while the control group will simply be send home without receiving a placebo intervention. Finally, publishing this protocol, which specifies all outcomes, will prevent selective reporting bias. All outcomes of the Pleasure&Pregnancy-RCT will be assessed reliably. More specifically, ongoing clinical pregnancies are confirmed by ultrasound diagnosis and all included PROMs are assessed with valid and reliable questionnaires. Other strengths of the Pleasure&Pregnancy-RCT are the power calculation, intention-to treat analysis and the standardized format of the intervention. This large scale RCT was not preceded by a pilot-RCT. The feasibility of our P&P-program was, however, optimized by involving experienced professionals and patients in the development of the program. For example, a timeline with a gradual build was chosen for the P&P-program as sexologists wanted to increase the intimacy level of the sensate focus exercises gradually and as interviewed patients shared that their need for self-management strategies increases over time.

The Pleasure&Pregnancy-program is a comprehensive educational program [53], which includes information, couple communication, sensate focus and mindfulness exercises and interaction. The Pleasure&Pregnancy-RCT will primarily test the hypothesis that this program increases ongoing pregnancy rates when compared to EM. If it is effective, it will be interesting to find out which of its elements contribute to this effect via which pathway. Assessing PROMs prior to, during and at the end of the Pleasure&Pregnancy-program and using web-based tracking to follow-up couples' adherence to the program, will help us disentangle the pathway. We expect the Pleasure&Pregnancy-program to work by increasing pleasurable sex, which increases coital frequency, which in turn increases ongoing pregnancy rates. It is, however, also biologically plausible that improved sexual arousal and pleasure have a direct positive effect on ongoing pregnancy rates. More specifically, in men, orgasms following higher levels of sexual arousal have been associated with better sperm quality.[58] In women, orgasms may enhance passive and active sperm transport. [59] [60] Female sexual arousal also enhances lubrication of the vagina, neutralizes pH and increases perivaginal vasocongestion, which in turn improves mobility and survival of spermatozoa.[61] [62] Vaginal dryness is associated with the use of commercial lubricants, of which some compromise sperm quality. [23] [63]

If this RCT proves that the Pleasure&Pregnancy-program is effective, we will advise to offer an interactive educational program as first line treatment in couples with (relatively) unexplained subfertility before embarking on medically assisted reproduction. As more couples would be conceiving naturally, the Pleasure&Pregnancy-program would decrease the 67% of couples returning for MAR after having continued to attempt natural conception for six months. [64] This would be highly relevant as MAR is associated with many drawbacks including significant costs, treatment burden and increased probability of multiple pregnancy, obstetric and perinatal complications, congenital abnormalities and long-term health risks for offspring. [65-72] If the Pleasure&Pregnancy-program increases the number of couples conceiving naturally and/or improves sexual functioning, it would be worthwhile to consider also offering it to couples with other infertility diagnoses at other treatment stages, or even to couples who are interested to improve their sexual functioning. The eHealth format of the Pleasure&Pregnancy-program will facilitate its low-cost wide-spread implementation.

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Authors' contribution

EAFD, IC, TMD, CBL, EL, SR and MW designed the trial, developed the protocol and applied for funding. EAFD, IC and FD applied for ethical approval and implemented the logistics of the trial. All authors read, revised and approved the final manuscript.

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Competing interests

The authors declare to have no financial or non-financial conflicts of interest.

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Other declarations

The following other declarations are not applicable to this manuscript: consent for publication, availability of data and material and endnotes.

List of abbreviations

BIA: budget impact analysis; CEA: cost-effectiveness analysis; MAR: medically assisted reproduction; PROMS: Patient reported outcome measures; RCT: randomized controlled trial.

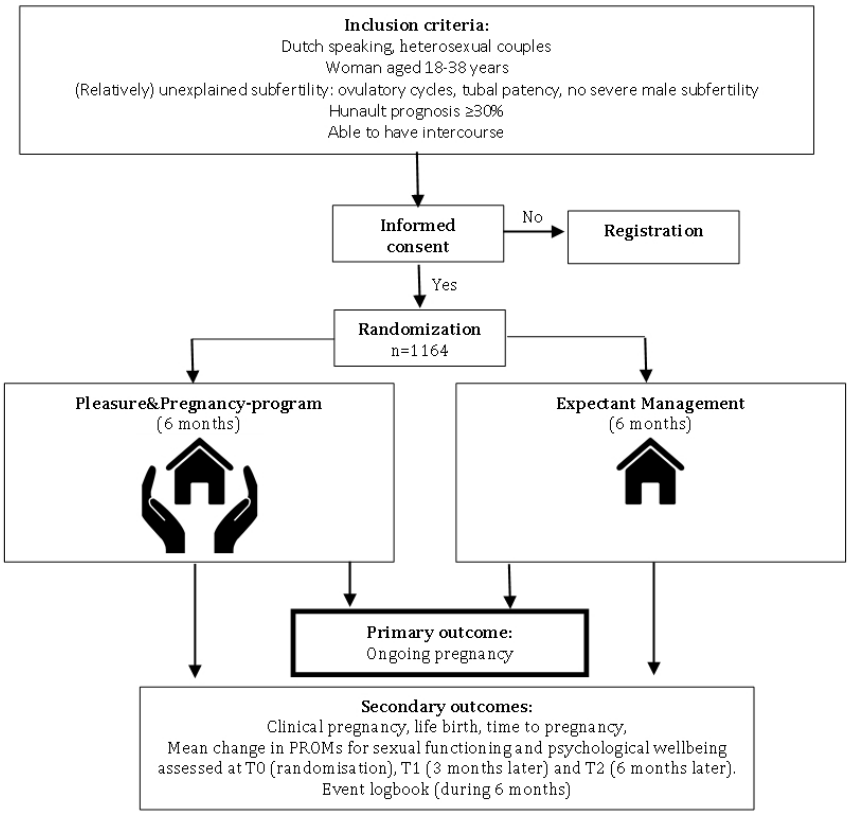
Availability of data and material

A link to the randomization program and data management program can be found on the study website. As well as the most recent protocol version and other study documents. [15] Upon completion of the data collection, this RCT will be analyzed by the Pleasure&Pregnancy researcher team. The Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology will facilitate data-sharing with other interested Dutch research groups wishing to perform additional analysis.

Figure legend:

Figure 1. Flow-chart of the Pleasure & Pregnancy-RCT

Figure I. Flow-chart of the Pleasure&Pregnancy-RCT



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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1, line 2-4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 2, line 72 and page 11, line 438
	2b	All items from the World Health Organization Trial Registration Data Set	Page 1-18
Protocol version	3	Date and version identifier	Page 18, line 912-914
Funding	4	Sources and types of financial, material, and other support	Page 18, line 891-894
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 18, line 886-889
	5b	Name and contact information for the trial sponsor	Page 1, line 13-14
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Not applicable, p19 line 687-689

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 18, line 912-918
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 4, line 84-114
	6b	Explanation for choice of comparators	Page 4, line 92-96
Objectives	7	Specific objectives or hypotheses	Page 5, line 124-128
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 5, line 130-136
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 5, line 143-150
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 5+6, line 152-177
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 7, line 233-266
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 8, line 301-302
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 7, line 244-245

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 6, line 173-177
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 7+8, line 268-305
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 7, line 249-252 + page 8 307-311 + figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 6, line 180-187
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 6, line 188-204
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 5, line 130-133
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 5, line 134-136
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 5, line 130-136 and Page 6 line 206-212
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 5, line 134-136

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 7-8-9, table 1
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 8, line 301-304
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 18, line 913-919
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 10, line 375-394
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 10, line 375-394
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 10, line 375-394
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Not applicable
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 10, line 377-379
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 10, line 377-379
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 18, line 913-919
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 11, line 334-442
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not applicable
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 6, line 206-212
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 6, line 206-212
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 18, line 897-898
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 18, line 911-917

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 10-11, 418-332
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 18, 887-890
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Page 18, line 913-919
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.