BMJ Open

Efficacy of group biofeedback treatment on Hyperemesis Gravidarum with psychosomatic symptoms diagnosed with the revised version of Diagnostic Criteria for Psychosomatic Research (DCPR-R): study protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051295
Article Type:	Protocol
Date Submitted by the Author:	17-Mar-2021
Complete List of Authors:	cui, xuelian; changzhou maternity and child healthcare hospital, Department of Healthcare Cao, Jianxin; Third Affiliated Hospital of Soochow University, Department of gastroenterology Rafanelli, Chiara; University of Bologna, Department of Psychology Zhu, Boheng; University of Bologna, Department of Psychology; DepartmenPeking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, Department of Psychological Medicine Gostoli, Sara; University of Bologna, Department of Psychology
Keywords:	Depression & mood disorders < PSYCHIATRY, Adult psychiatry < PSYCHIATRY, PREVENTIVE MEDICINE

Title page

Title: Efficacy of group biofeedback treatment on Hyperemesis Gravidarum with psychosomatic symptoms diagnosed with the revised version of Diagnostic Criteria for Psychosomatic Research (DCPR-R): study protocol for a randomized controlled trial

Xuelian Cui,[1] Jianxin Cao,[2] Chiara Rafanelli,[3] Boheng Zhu,[3] Sara Gostoli[3]

Author affiliations

[1]Department of Healthcare, Affiliated Changzhou Maternity and Child Healthcare Hospital, Nanjing Medical University, Changzhou, China.

[2]Department of Gastroenterology, The Third Affiliated Hospital, Soochow University, Changzhou, China

[3]Department of Psychology, University of Bologna, Bologna, Italy

Correspondence to

Jianxin Cao; drtsao123@sina.cn.

Efficacy of group biofeedback treatment on Hyperemesis Gravidarum with psychosomatic symptoms diagnosed with the revised version of Diagnostic Criteria for Psychosomatic Research (DCPR-R): study protocol for a randomized controlled trial

Xuelian Cui,[1] Jianxin Cao,[2] Chiara Rafanelli,[3] Boheng Zhu,[3] Sara Gostoli[3]

Author affiliations

[1]Department of Healthcare, Affiliated Changzhou Maternity and Child Healthcare Hospital, Nanjing Medical University, Changzhou, China.

[2]Department of Gastroenterology, The Third Affiliated Hospital, Soochow University, Changzhou, China

[3]Department of Psychology, University of Bologna, Bologna, Italy

Correspondence to

Dr Jianxin Cao; drtsao123@sina.cn

ABSTRACT

Introduction

Hyperemesis Gravidarum (HG) is a condition characterized by dehydration, electrolyte imbalance, lack of nutrition, and at least 5% loss in body weight, occurring in the first half of pregnancy. The aim of this trial is to examine the efficacy of group biofeedback treatment on HG patients with psychosomatic symptoms, which will be evaluated through the revised version of Diagnostic Criteria for Psychosomatic Research (DCPR-R).

Methods and analysis

In this single-blinded randomized controlled clinical trial, sixty-eight HG patients diagnosed with

at least one psychosomatic syndrome by DCPR-R and aged 18-40 years, will be randomised (1:1) into two arms: experimental group, which will undergo to group biofeedback treatment, psycho-education and treatment as usual (TAU); and control group, which will undergo psycho-education and TAU only. The primary outcomes will be the improvements of the severity of nausea/vomiting, quality of life and heart rate variability. The secondary outcomes will include days of hospitalization, repeated hospitalization and laboratory investigations. This is the first study to evaluate the psychosomatic symptoms of HG patients with the revised version of the Diagnostic Criteria for Psychosomatic Research (DCPR-R), which represent a dedicated tool for assessing psychosomatic symptoms. This study will show the effect of group biofeedback, a noninvasive and harmless intervention for both pregnant women and fetus, on the severity of nausea/vomiting among HG patients. The results are expected to contribute to a sensitive diagnostic criteria of psychosomatic symptoms for HG patients, and a tailored protocol of group biofeedback intervention for HG patients with psychosomatic syndromes.

Ethics and dissemination

This study has received ethic approval from the Nanjing Medical University (NO. 2019/491, granted 22 February 2019). All the data will be uploaded to ResMan raw data sharing platform of China Clinical Trial Registry. Study outcomes will be disseminated through peer-reviewed publications and academic conferences, and used to confirm a tailored biofeedback intervention for HG patients with psychosomatic symptoms.

Trial registration number

Chinese Clinical Trial Registry Number: ChiCTR2000028754. Registered on 1 January 2020.

Strengths and limitations of this study

► This is the first study to evaluate the psychosomatic symptoms of HG patients with the revised version of the Diagnostic Criteria for Psychosomatic Research (DCPR-R), which represent a dedicated tool for assessing psychosomatic symptoms.

►This study will show the effect of group biofeedback, a noninvasive and harmless intervention for both pregnant women and fetus, on the severity of nausea/vomiting among HG patients.

►The results are expected to contribute to a sensitive diagnostic criteria of psychosomatic symptoms for HG patients, and a tailored protocol of group biofeedback intervention for HG patients with psychosomatic syndromes.

►A limitation is that it is not a placebo intervention control study, therefore we cannot exclude the placebo effect of the biofeedback instrument.

BACKGROUND

Hyperemesis Gravidarum (HG) is a condition characterized by dehydration, electrolyte imbalance, lack of nutrition, and at least 5% loss in body weight[1]. HG rates in pregnant women range from 0.3% to 3%, and it is considered one of the most important pregnancy-related complications[2]. HG appears in the first half and can last throughout the pregnancy, although the symptoms usually resolve within 20 gestational weeks [2]. This condition generally requires frequent visits to the emergency room and repeated hospitalizations for intravenous hydration, which severely compromise quality of life (QoL) [3]. Hospitalization rates for HG vary between populations: from 1% to 2% in the United States[4], 10.8% in Shanghai, China [5]. The complications of HG include multiple nutritional deficiencies, Wernicke's encephalopathy, esophageal laceration, terminate the desired pregnancy and fear of subsequent pregnancy, preterm birth and low birth weight[2].

The etiology and pathogenesis of HG remain uncertain, but should be multi-factorial with biologic, psychological and socio-economic antecedents [6], including maternal endocrine disorders, hepatic abnormalities, gastrointestinal dysfunction, pituitary axis malfunction, autonomic nervous dysfunction, and psychosomatic factors[7]. The Diagnostic Criteria for Psychosomatic Research (DCPR) were developed to diagnose psychological disorders that could have a negative prognostic role in medical illnesses, but are not detectable with the use of Diagnostic and Statistical Manual of Mental Disorders (DSM) – based on traditional psychiatric criteria [8]. The DCPR have demonstrated an excellent predictive validity for psychosocial functioning and treatment outcomes in several medical settings, including oncology[9], dermatology[10], endocrinology[11], cardiology[12, 13], gastroenterology[14], and immune system [15]. In 2017, a revised version of the DCPR (DCPR-R) was published[16] . To date, no study has examined the prevalence of the DCPR syndromes in HG.

Group biofeedback is a method to process in-vivo information related to psychological and

physiological activities, such as muscle tension, skin temperature, heart rate, blood pressure, brain waves, for multiple patients (2-20) at the same time [17]. Its working principles include heart rate variability biofeedback (HRVB), abdominal breathing and Jacobson's muscle relaxation [18]. Biofeedback constitutes a noninvasive psychological intervention, which showed its efficacy in the treatment of asthma, chronic obstructive pulmonary disease, irritable bowel syndrome, cyclic vomiting, recurrent abdominal pain, fibromyalgia, cardiac rehabilitation, hypertension, chronic muscle pain, pregnancy induced hypertension, depression, anxiety, post-traumatic stress disorder [19]. It was also used to decrease perinatal anxiety and depression in the third trimester [20] and psychological stress during the early postpartum period[21]. To our knowledge, there is no information about the efficacy of group biofeedback on psychosomatic symptoms in the first and early second trimester of pregnancy [22].

The present study aims to explore the efficacy of group biofeedback treatment on nausea/vomiting and quality of life of HG patients with psychosomatic symptoms. Compared to control group, we hypothesize that the experimental group will have a significant improvement on the quality of life, severity of nausea/vomiting, HRV index, days of hospital admission, number of repeated HG treatments, and laboratory investigations after 2-week group biofeedback intervention.

METHODS

Study design

This is a single-blind, randomized controlled trial. Change in primary outcome will be measured from baseline to 2-week post intervention, while change in secondary outcomes will be measured from baseline to 20weeks follow-up. All personal data will be treated confidentially. Protocol Version 1.1, dated 1 March 2017.

Participants

Patients will be recruited at the Department of Gynecology of Changzhou Maternity and Child Healthcare Hospital affiliated with Nanjing Medical University, Changzhou, China. Approximately 190 HG patients were hospitalized yearly at this department. We expect to recruit 68 patients diagnosed with at least one psychosomatic syndrome.

A socio-demographic interview, including information on age, previous miscarriage, gestational

age when vomiting started (weeks), days of vomiting at admission, hyperemesis in a previous pregnancy, income, level of education, employment status, medical history, weight at admission, will be administered at baseline.

Eligibility criteria

1. Diagnosis of HG in a singleton pregnancy documented by the presence of severe vomiting (more than 3 times per day without any other obvious cause), an inability to maintain oral nutrition, weight loss of more than 3 kilograms and at least one positive ketonuria test [2].

2. At least one psychosomatic syndrome according to the evaluation of DCPR-R system[16].

3. No evidence of antenatal bleeding, no antibiotic treatment, H2 blockers or proton pump inhibitors in the previous month[23].

4. Patients without any psychiatric comorbidity (schizophrenia, bipolar disorder, substance dependence, personality disorder), as ascertained from the clinical records consultation.

5. Age ranging from 18 years to 40 years old.

Exclusion criteria

Exclusion criteria include fetal anomaly, antenatal bleeding, multiple pregnancy, systemic disease, hyperthyroidism, hepatic disorders, urinary tract infections or intracranial disorders, gastrointestinal diseases, and difficulty to understand the questions and follow the instruction.

Randomization and blinding

Participants who will be eligible in the screening phase and will agree to sign the consent form, will be randomly assigned to the experimental group or control condition. The random sequence numbering will be carried out by a computer program (the Random Allocation Software 2.0), with an allocation ratio of 1:1. An independent researcher who will not join other procedures, will perform the randomization process in order to avoid bias.

The researcher responsible for the assessment will be blinded to all intervention groups. Participants will be informed that two different intervention techniques will be tested. The interventions will be scheduled in different times and days, so that participants will not have contact between groups. Data collection will be conducted by a blinded and trained researcher.

Finally, the researcher responsible for statistical analyses will be blinded too. Once the study will be concluded, this researcher will receive a dataset with all necessary data without identification of participants and groups.

Intervention

Three interventions that will be performed in the two groups: group biofeedback intervention, psycho-education and treatment as usual (TAU). A nurse who received professional biofeedback training will administer the group biofeedback. The goal of this program is to help participants to learn diaphragmatic breathing techniques, Jacobson's muscle relaxation and guided Imagery, while monitoring heart rate variability (HRV). The intervention will include ten sessions delivered every working day in two weeks. Each session will last about 30-40 minutes, in a group setting (2-4 participants).

● Session 1. First, teach patients about the mechanism of group biofeedback, the science behind the technique, and potential benefits and outcomes of its use. Second, measure baseline HRV in 5-minute time interval. Third, teach participants the slow breathing at resonance frequency about 6.5 to 6 breaths/minute, for ten minutes. Finally, guide participants how to tense and relax larger groups of muscles: (a) feet and legs; (b) stomach and chest; (c) arms and hands; (d) shoulders, back, and neck; and (e) face. Muscle relaxation will last ten minutes.

● Session 2. First, measure the HRV in 5-minute time interval. Second, conduct the slow breathing at resonance frequency about 6 breaths/minute, for ten minutes. Finally, implement the progressive muscle relaxation and body scanning to manage tension for ten minutes.

● Session 3-5. Tell the participants to do as the session 2. In addition, participants are instructed to practice resonance frequency breathing as a 10-minute daily homework.

● Session 6-9. Tell the participants to do as sessions 3-5. Additionally, after muscle relaxation, ask the participants to watch love, compassion, and forgiveness images on the computer screen, and encourage them to enter a calm, safe, content, and relaxed state through the guided imagery. This costs 10 minutes.

● Session 10. First, measure the HRV in 5-minute time interval as the post-intervention. Second, ask patients to think about three questions: "what have you experienced during the intervention", "what you have learned from the intervention", "which feedback exercise you will practice by

yourself in the future". Tell patients they can do the exercises routinely, or when they just realize that they are overly emotional or dysfunctional. Finally, repeat the three exercises for the last time. The psycho-education includes explanations of the detrimental effect of psychosomatic symptoms on the treatment of HG, of maternal anxiety and depression on both the fetus and the infant (i.e., behavioral problems, learning difficulties, psychiatric illness in the offspring, and premature termination of pregnancy). In addition, participants will also be told that and social interactions can help release anxiety and depression. Individual psychoeducation will be implemented only once for 30 minutes before each participant will be assigned either to experimental group or control group.

TAU will involve any recommendation given to the participants by their gynecologist, including parenteral antiemetic medications, electrolyte repletion, and nutritional support. Patients in both groups will be asked to follow gynecologists' recommendations, and are discharged once they are rehydrated and capable of maintaining adequate oral intake, which depend on the judgement of the gynecologist.

All the three interventions will be performed in the experimental group. Before patients will be involve in the group, they will receive the psychoeducation once for 30 minutes, then 10 sessions of group biofeedback and TAU, for two weeks. If patients will be discharged within the two weeks, they will be asked to come back to hospital every working day to complete the rest of the treatment.

In the control group, patients will receive the psycho-education once for 30 minutes before they will be allocated in the group, and then TAU only. They can be discharged once they will be rehydrated and capable of maintaining adequate oral intake. They will be asked to measure HRV once again after 2 weeks, whether discharged or hospitalized.

Primary outcome measures

Psychosomatic syndromes

A revised version of the Semi-Structured Interview based on Diagnostic Criteria for Psychosomatic Research-Revised (DCPR-R) [16]will be used to assess the presence of psychosomatic syndromes. DCPR-R have a modular structure including 4 domains (i.e. stress, illness behavior, psychological manifestation, personality), and allow the formulation of 14

diagnostic rubrics: allostatic overload, health anxiety, disease phobia, hypochondriasis, thanatophobia, illness denial, persistent somatization, alexithymia, conversion symptoms, anniversary reaction, somatic symptoms secondary to a psychiatric disorder, demoralization, demoralization with hopelessness, irritable mood, type A behavior, and alexithymia. The interview has 79 yes/no items and focuses on the past 12 months. It showed a good interrater reliability, ranging from 0.69 to 0.97[24]. Skip instructions are provided and some questions do not need to be asked. Some items can be completed based on the interviewer's observation and clinical judgement without specific questioning. If participants will be discharged in less than two weeks, they will be reached by telephone to undergo the interview.

Severity of nausea/vomiting

The modified Pregnancy-Unique Quantification of Emesis and Nausea (modified-PUQE)[25], a 3-item self-rating scale that incorporates three dimensions (i.e. nausea, vomiting, retching), will be used to assess the severity of nausea /vomiting. It represents a valid index for the assessment of nausea/vomiting severity and its use is justified to assess global nausea/vomiting severity in the first trimester of pregnancy. The respondents are asked to indicate - on a 5-point Likert scale - the extent to which they agree with each statement. The sum score may range from 3-15. 3-6 represents mild nausea/vomiting; 7-12, moderate nausea/vomiting; and 13-15, severe nausea/ vomiting. The infraclass correlation coefficient was 0.71, and the severity of nausea/vomiting that was measured by the modified-PUQE was associated with QoL[25].

HRV index

The biofeedback system (Heartmath, VISHEE, Nanjing) is used to monitor and record the HRV index, including the standard deviation of normal--to-normal intervals (SDNN) between adjacent heartbeats, high frequency (HF) and low frequency (LF) [26] HRV, and the ratio between LF and HF (LF/HF). SDNN represents the amount of variability in heartbeat intervals for a given time period; in this study 5-minute time intervals at pre-intervention and post-intervention are used [27]. The higher values of SDNN, the better health outcomes. HF HRV reflects parasympathetic activity and typically corresponds to the range between 0.15 and 0.40 Hz [28, 29]. LF HRV is influenced by both the sympathetic and parasympathetic systems, baroreflex activity and typically corresponds to the range between 0.05 and 0.15 Hz.

Quality of life (QoL)

Short-Form Health Survey with the standard 12-item version (SF-12) [30] will be used to measure QoL. This shorter version of the commonly used SF-36 yields 2 summary measures of physical

and mental health. Summary measures will be calculated by adding the scores of the 12 items, with a range from 0-100; higher scores represent better QoL. The relative validity ranged from 0.43-0.93 (median 0.68) for physical health, and 0.60-1.07 (median 0.84) for the mental health[30].

Secondary outcome measures

Days of hospitalization

Length of hospitalization after enrollment, as recorded the patients' hospitalization days between pre-intervention and the discharge from the hospital. Patients are discharged once they are rehydrated and capable of maintaining adequate oral intake, upon the decision of their gynecologists. The longer length of hospital stays, the higher the economic costs are.

Re-hospitalization for HG

The repeated hospitalization for HG after the intervention until 20-week gestation, as measured follow-up after their first discharge from the hospital. All the participants will be asked by telephone whether they have received the HG treatment again after discharge, up to 20-week gestation.

Laboratory investigations

Ketonuria, renal function, serum electrolytes and full blood count results represent measures of severity of HG during hospitalization. All the participants will undergo the laboratory investigations at T0 and T1.

Monitoring

On the basis of the no risk of harms associated with the non-pharmaceutical intervention in this Clinical Trials of an Investigational Medicinal Product (CTIMP) trial, no interim analysis or data monitoring committee is planned.

Confidentiality

All data will be anonymized to ensure patient confidentiality is protected. A unique research number will be used to identify the participants' data in the database. Data will be kept securely and only the investigators have access to the data.

Evaluations

The participants in both groups will be evaluated with the SSI based on DCPR-R, SCID for DSM 5, modified-PUQE, HRV index, QoL and laboratory investigations before the treatment (T0), at the end of the treatment (i.e., two weeks later) (T1). Days of hospitalization and number of repeated hospitalization will be assessed as well at T2.

Participant timeline

Participants are identified in the Department of Gynecology according to eligibility criteria and exclusion criteria by research staff. Following gaining written consent, participants are immediately randomized to the control group or the intervention group. For those patients randomized to the control group, psychoeducation and TAU will be administered. For the intervention group, patients will receive 2-week biofeedback intervention additionally. The assessment of DCPR-R, modified-PUQE, HRV, QoL, and laboratory investigations will conduct before and after 2-week treatment, days of hospitalization and re-hospitalization for HG will be collected until 20 gestation week for both groups.

Sample size

Based on a previous trial about psychotherapy on nausea and vomiting of pregnant women, the SD of modified-PUQE in nausea and vomiting pregnant women is 3 [31]. To detect a medium effect size (f=.25) at the statistical power of .90 based on a two sided significance level .05, a minimum sample of 44 participants will be required. Given an attrition rate of 35%, as observed in other biofeedback intervention trials [32] , it is expected to recruit at least 68 patients. G*Power3.1 has been used to calculate the sample size.

Patient and Public Involvement

Gynecology doctors from the Department of Gynecology of Changzhou Maternity and Child Healthcare Hospital were consulted in the development of the trial and reviewed the protocol. They provided valuable insights which led to considerations of ethical issues as well as feasibility, which resulted in the changes in inclusion criteria, outcome measures and continued treatment after the end of intervention. They introduced the project to their patients who will decide for themselves to participate in the research or not. The intervention fee of the experimental group would be paid by the two funding. We plan to inform the trial participants of the final results if requested.

Data access

Full access to the dataset will be held by the principal investigators, coinvestigators and statistician only.

Statistical analysis

All the data will be analyzed with the Statistical Package for Social Science 22.0 (SPSS 22.0). Repeated Measures ANOVA will be implemented to evaluate between and within groups changes in modified-PUQE, HRV index, QoL (primary outcome), and the laboratory investigations (secondary outcome). Independent sample t test will be used to analyze differences concerning length of hospitalization (measured in days) and number of repeated hospitalization between two groups. Pearson Chi-squared tests and independent samples t tests will be performed to assess statistical differences on clinical and socio-demographic characteristics between two groups. In addition, Pearson Chi-squared tests will be used to assess the rate of moderate and severe nausea/vomiting in both groups pre and post intervention, respectively. Missing data will be dealt by means of multiple imputation procedures. The differences will be considered significant with a p value ≤ 0.05.

DISCUSSION

The DSM-5 has been regarded as the gold standard of psychiatric evaluation [33]. Anxiety and depression were common in the first trimester among HG women assessed during their first hospitalization, with caseness rates of 20.6%~46.9% and 29.2%~47.8% respectively[34], 36.3% and 22.1% from a longitudinal study of Chinese women in Hong Kong[35].

However, the methodological flaws in studies have left the concept that anxiety and depression as a cause or outcome of HG unsupported by evidence[36], and psychiatric diagnoses are not highly represented among women with HG who feel less overall healthy during the pregnancy [37]. First, the bulk of the existing data does suggest that even if women with HG feel less generally healthy during the pregnancy, psychiatric diagnoses are not over-represented longitudinally[37]. Most of the previous studies[38] used self-reporting scales (Beck Anxiety Inventory, Beck Depression Inventory, Hospital Anxiety and Depression Scale, Edinburgh Postnatal Depression Scale, Spielberger Anxiety Index) to screen and diagnose anxiety and depression, without structured psychiatric interview and observer-rated evaluation. Second, in the psychiatric medicine literature, demoralization during a medical illness is often misdiagnosed with depression[37]. Even though some symptoms can overlap with depression, patients with demoralization will have significant mood improvement when their medical circumstances improve, and this characteristic seems particularly applicable to women with HG and should diagnostically be considered first and

foremost [37]. Third, psychosomatic aspects of HG has been proposed since 1984 [39], but there is still no appropriate assessment tool performed in the clinical practice with these patients.

Compared with DSM-5, DCPR have been regarded as a more sensitive tool in detecting psychosomatic suffering [40, 41], and showed their clinical utility in subtyping medical patients, identifying subthreshold or undetected syndromes, evaluating the burden of somatic syndromes, predicting treatment outcomes, and identifying risk factors[15].

It is possible that in some women, vomiting becomes a conditioned or anticipatory response and – for this reason - it would be amenable to interventions such as psychotherapeutic approaches[42]. Literature showed positive results obtained with hypnotherapy [43] in treating nausea/vomiting in HG women. However, these findings were obtained from case series and did not include control groups, which makes difficult to differentiate true treatment benefits from normal recovery. Additionally, some patients could experience contradictory arousal effects deriving from some relaxation exercises in psychotherapy, which could make them more nervous and anxious[44, 45] . Therefore, in this study, group biofeedback is selected as an intervention that allows patients to monitor their own emotional state in real time, during the treatment.

Biofeedback has been used to reduce perinatal anxious and depressive symptoms, and its safety for pregnant women is beyond doubt[21]. The three working principles (i.e., HRV, Jacobson's muscle relaxation and guided imagery) have been applied to improve physiological and psychological functions[46]. HRV, a key marker of parasympathetic functioning and a potent predictor of physical morbidity and mortality[47], involves learning how to breathe at a resonance frequency rate, typically about 6 breaths per minute. Autonomic nervous dysfunction is also considered to be one of the possible etiology for HG [7]. HRV biofeedback training increases baro-reflexes and helps people develop healthier breathing patterns, and it permits the upregulation of the body ability to balance environmental change and physiological needs by improving baroreceptor and parasympathetic function [32]. Jacobson's progressive muscle relaxation (PMR) constitutes a systematic technique for achieving a deep state of relaxation through a progressive tensing and relaxation of various muscle groups. Application of PMR has been shown to reduce stress and anxiety, to improve symptoms such as tension headaches and insomnia, and to make a positive contribution to adjuvant therapy in cancer, chronic pain management in inflammatory arthritis, and irritable bowel syndrome[48]. Finally, guided imagery represents a tool to encourage subjects to enter a safe, calm, content, and relaxed state. A positive imagery activity is verbally introduced by the computer as a narration of thoughts and suggestions that guide the

listener's imagination. Psycho-neuro-immunological theories propose that the psychological response to guided imagery may downregulate the hypothalamic-pituitary-adrenal axis, resulting in a reduced stress response, increased immune function, and greater sense of well-being[49].

Compared with the control group, participants in the experimental group are expected to experience a significant decrease in the severity of nausea and vomiting, improvement of HRV index and laboratory results, better quality of life, shorter hospitalization stays, and lower frequency re-hospitalization for HG after the intervention. Findings from this study would contribute to a sensitive diagnostic criteria of psychosomatic symptoms for HG patients, and the development of a tailored protocol of group biofeedback intervention to improve HG-related symptoms among both inpatients and outpatients with psychosomatic syndromes.

Trial status

This study describes he first version of the protocol (V1.0). Patient recruitment is currently ongoing. If the protocol needs to be amended, the relevant parts of the study will be updated, and the changes will be recorded in the clinical trials registry (chictr.org.cn. ChiCTR2000028754). Due to the impact of COVID-19, our related researches have been severely affected, and will be appropriately postponed. The first patient has been enrolled on August 20,2020, and it is expected to finish by the end of 2022.

Abbreviations

DCPR-R: the revised version of Diagnostic Criteria for Psychosomatic Research; HG: Hyperemesis Gravidarum; TAU: treatment as usual; QoL: quality of life; DSM: Diagnostic and Statistical Manual of Mental Disorders; HRVB: heart rate variability biofeedback; modified-PUQE: modified Pregnancy-Unique Quantification of Emesis and Nausea; SDNN: standard deviation of normal--to-normal intervals; SF-12: Short-Form Health Survey with the standard 12-item version; CTIMP: Clinical Trials of an Investigational Medicinal Product;

Acknowledgements

The authors would like to thank patients and their doctors in the obstetrics and gynecology department at Changzhou Maternity and Child Healthcare Hospital Affiliated with Nanjing Medical University for making the study possible.

Authors' contributions

XC conceived the study and is the chief and principal investigator. XC and BZ designed the study. XC and SG wrote the protocol. JC and CR reviewed the manuscript. All authors read and approved the final manuscript.

Funding

The study did not receive funding for development. The PI is supported by the Jiangsu Natural Science Foundation (BK20190163) and China Postdoctoral Science Foundation (NO.243555). The organization that supports the PI did not and will not play a role in the study design, the collection, management, analysis and interpretation of the data.

Availability of data and materials

The datasets are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval

Prior to commencing the study, this study has been evaluated and approved by the Reasearch Ethical Board of the Nanjing Medical University (NO. 2019/491, granted 22 February 2019) in China.

Reference

1 King TL, Murphy PA: Evidence-based approaches to managing nausea and vomiting in early pregnancy. *J Midwifery Womens Health* 2009; 54:430-44.

2 Gynecology ACoOa: ACOG (American College of Obstetrics and Gynecology) Practice Bulletin: nausea and vomiting of pregnancy. *Obstet Gynecol* 2004; 103:803-14.

3 Eliakim R, Abulafia O, Sherer DM: Hyperemesis gravidarum: a current review. *Am J Perinatol* 2000; 17:207-18.

4 Jarnfelt-Samsioe A: Nausea and vomiting in pregnancy: a review. *Obstet Gynecol Surv* 1987; 42:422-7.

5 Zhang J, Cai WW: Severe vomiting during pregnancy: antenatal correlates and fetal outcomes. *Epidemiology* 1991; 2:454-7.

6 Verberg MF, Gillott DJ, Al-Fardan N *et al*: Hyperemesis gravidarum, a literature review. *Hum Reprod Update* 2005; 11:527-39.

7 Bailit JL: Hyperemesis gravidarium: Epidemiologic findings from a large cohort. *Am J Obstet Gynecol* 2005; 193:811-4.

8 Fava GA, Freyberger HJ, Bech P *et al*: Diagnostic criteria for use in psychosomatic research. *Psychother Psychosom* 1995; 63:1-8.

9 Grassi L, Sabato S, Rossi E *et al*: Use of the diagnostic criteria for psychosomatic research in oncology. *Psychother Psychosom* 2005; 74:100-7.

10 Picardi A, Porcelli P, Pasquini P *et al*: Integration of multiple criteria for psychosomatic assessment of dermatological patients. *Psychosomatics* 2006; 47:122-8.

11 Sonino N, Peruzzi P: A psychoneuroendocrinology service. *Psychother Psychosom* 2009; 78:346-51.

12 Rafanelli C, Roncuzzi R, Milaneschi Y *et al*: Stressful life events, depression and demoralization as risk factors for acute coronary heart disease. *Psychother Psychosom* 2005; 74:179-84.

13 Rafanelli C, Sirri L, Grandi S *et al*: Is depression the wrong treatment target for improving outcome in coronary artery disease? *Psychother Psychosom* 2013; 82:285-91.

14 Cao J, Ding L: Psychosomatic Practice in Gastroenterology: New Insights and Models from China. *Psychother Psychosom* 2019; 88:321-26.

15 Porcelli P, Guidi J: The Clinical Utility of the Diagnostic Criteria for Psychosomatic Research: A Review of Studies. *Psychother Psychosom* 2015; 84:265-72.

16 Fava GA, Cosci F, Sonino N: Current Psychosomatic Practice. *Psychother Psychosom* 2017; 86:13-30.

17 Fisher CJ, Moravec CS, Khorshid L: The "How and Why" of Group Biofeedback for Chronic Disease Management. *Appl Psychophysiol Biofeedback* 2018; 43:333-40.

18 Aritzeta A, Soroa G, Balluerka N *et al*: Reducing Anxiety and Improving Academic Performance Through a Biofeedback Relaxation Training Program. *Appl Psychophysiol Biofeedback* 2017; 42:193-202.

19 Lehrer PM, Gevirtz R: Heart rate variability biofeedback: how and why does it work? *Front Psychol* 2014; 5:756.

20 Beckham AJ, Greene TB, Meltzer-Brody S: A pilot study of heart rate variability biofeedback therapy in the treatment of perinatal depression on a specialized perinatal psychiatry inpatient unit. *Arch Womens Ment Health* 2013; 16:59-65.

21 Kudo N, Shinohara H, Kodama H: Heart rate variability biofeedback intervention for reduction of psychological stress during the early postpartum period. *Appl Psychophysiol Biofeedback* 2014; 39:203-11.

22 Pinter A, Szatmari S, Jr., Horvath T *et al*: Cardiac dysautonomia in depression - heart rate variability biofeedback as a potential add-on therapy. *Neuropsychiatr Dis Treat* 2019; 15:1287-310.

23 Annagur BB, Tazegul A, Gunduz S: Do psychiatric disorders continue during pregnancy in women with hyperemesis gravidarum: a prospective study. *Gen Hosp Psychiatry* 2013; 35:492-6.

24 Galeazzi GM, Ferrari S, Mackinnon A *et al*: Interrater Reliability, Prevalence, and Relation to ICD-10 Diagnoses of the Diagnostic Criteria for Psychosomatic Research in Consultation-Liaison Psychiatry Patients. *Psychosomatics* 2004; 45:386-93.

25 Lacasse A, Rey E, Ferreira E *et al*: Validity of a modified Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) scoring index to assess severity of nausea and vomiting of pregnancy. *Am J Obstet Gynecol* 2008; 198:71 e1-7.

26 Sgoifo A, Carnevali L, Alfonso Mde L *et al*: Autonomic dysfunction and heart rate variability in depression. *Stress* 2015; 18:343-52.

27 Vaschillo EG, Vaschillo B, Lehrer PM: Characteristics of resonance in heart rate variability stimulated by biofeedback. *Appl Psychophysiol Biofeedback* 2006; 31:129-42.

28 Karavidas MK, Lehrer PM, Vaschillo E *et al*: Preliminary results of an open label study of heart rate variability biofeedback for the treatment of major depression. *Appl Psychophysiol Biofeedback* 2007; 32:19-30.

29 Kemp AH, Quintana DS, Felmingham KL *et al*: Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk. *PLoS One* 2012; 7:e30777.

30 Ware J, Jr., Kosinski M, Keller SD: A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; 34:220-33.

31 Shakiba M, Parsi H, Shikhi ZP *et al*: The Effect of Psycho-Education Intervention Based on Relaxation Methods and Guided Imagery on Nausea and Vomiting of Pregnant Women. *Journal of Family and Reproductive Health* 2019; 13:47-55.

32 Caldwell YT, Steffen PR: Adding HRV biofeedback to psychotherapy increases heart rate variability and improves the treatment of major depressive disorder. *Int J Psychophysiol* 2018; 131:96-101.

33 Previdi MC, Carotenuto P, Zito D *et al*: Noncoding RNAs as novel biomarkers in pancreatic cancer: what do we know? *Future Oncol* 2017; 13:443-53.

34 Tan PC, Vani S, Lim BK *et al*: Anxiety and depression in hyperemesis gravidarum: prevalence, risk factors and correlation with clinical severity. *Eur J Obstet Gynecol Reprod Biol* 2010; 149:153-8.

35 Lee AM, Lam SK, Sze Mun Lau SM *et al*: Prevalence, course, and risk factors for antenatal anxiety and depression. *Obstet Gynecol* 2007; 110:1102-12.

36 Fejzo MS: Measures of depression and anxiety in women with hyperemesis gravidarum are flawed. *Evid Based Nurs* 2017; 20:78-79.

37 Kim DR, Connolly KR, Cristancho P *et al*: Psychiatric consultation of patients with hyperemesis gravidarum. *Arch Womens Ment Health* 2009; 12:61-7.

38 Mitchell-Jones N, Gallos I, Farren J *et al*: Psychological morbidity associated with hyperemesis gravidarum: a systematic review and meta-analysis. *Bjog* 2017; 124:20-30.

39 Ringler M, Krizmanits A: Psychosomatic aspects of emesis gravidarum: somatic and

psychosocial status of females in early pregnancy. *Z Geburtshilfe Perinatol* 1984; 188:234-8.

40 Mangelli L, Bravi A, Fava GA *et al*: Assessing somatization with various diagnostic criteria. *Psychosomatics* 2009; 50:38-41.

41 Sirri L, Fava GA: Diagnostic criteria for psychosomatic research and somatic symptom disorders. *Int Rev Psychiatry* 2013; 25:19-30.

42 Madrid A, Giovannoli R, Wolfe M: Treating persistent nausea of pregnancy with hypnosis: four cases. *Am J Clin Hypn* 2011; 54:107-15.

43 Fuchs K, Paldi E, Abramovici H *et al*: Treatment of hyperemesis gravidarum by hypnosis. *Int J Clin Exp Hypn* 1980; 28:313-23.

44 Barlow DH: **Anxiety and its disorders: The nature and treatment of anxiety and panic (2nd ed)**. New York: Guilford Press; 2002.

45 Clark DM: **Cognitive-behavior therapy for psychiatric problems: A practical guide**, vol. Oxford University Press. Oxford University Press: New York; 1989.

46 Mcgrady A: Effects of group relaxation training and thermal biofeedback on blood pressure and related physiological and psychological variables in essential hypertension. *Biofeedback and self-regulation* 1994; 19:51.

47 Kemp AH, S. QD, R. QC *et al*: Major depressive disorder with melancholia displays robust alterations in resting state heart rate and its variability: implications for future morbidity and mortality. *Frontiers in Psychology* 2014; 5:1387.

48 Innes KE, Selfe TK, Vishnu A: Mind-body therapies for menopausal symptoms: a systematic review. *Maturitas* 2010; 66:135-49.

49 Roffe L, Schmidt K, Ernst E: A systematic review of guided imagery as an adjuvant cancer therapy. *Psychooncology* 2005; 14:607-17.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1/2/2020
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	13

contributorship			
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/a No sponsor
Roles and responsibilities: sponsor and funder	#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	N/a No sponsor
Roles and responsibilities: committees	#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)	N/a No committees
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	2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
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, non-inferiority, exploratory)	5
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	5
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)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
Interventions: modifications	#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)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	8
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)	11
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions	11

		supporting any sample size calculations	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
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	6
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	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate	10

		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	
Data collection plan: retention	#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	10
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	10
Statistics: outcomes	#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	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#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)	11
Methods: Monitoring			
Data monitoring: formal committee	#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	10
Data monitoring:	#21b	Description of any interim analyses and stopping	10

interim analysis		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	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
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)	N/a The first version, no amendments
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/a no
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	10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11

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	N/a
Dissemination policy: trial results	#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	1
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	1
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	1
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	6
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	10

Word count 3427

BMJ Open

Efficacy of group biofeedback treatment on Hyperemesis Gravidarum with psychosomatic symptoms diagnosed with the revised version of Diagnostic Criteria for Psychosomatic Research (DCPR-R): study protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-051295.R1
Article Type:	Protocol
Date Submitted by the Author:	20-Oct-2021
Complete List of Authors:	cui, xuelian; changzhou maternity and child healthcare hospital, Department of Healthcare Cao, Jianxin; Third Affiliated Hospital of Soochow University, Department of gastroenterology Rafanelli, Chiara; University of Bologna, Department of Psychology "Renzo Canestrari" Zhu, Boheng; Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Department of Psychological Medicine Gostoli, Sara; University of Bologna, Department of Psychology "Renzo Canestrari"
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Mental health
Keywords:	Depression & mood disorders < PSYCHIATRY, Adult psychiatry < PSYCHIATRY, PREVENTIVE MEDICINE

Title page

Title: Efficacy of group biofeedback treatment on Hyperemesis Gravidarum with psychosomatic symptoms diagnosed with the revised version of Diagnostic Criteria for Psychosomatic Research (DCPR-R): study protocol for a randomized controlled trial

Xuelian Cui,[1] Jianxin Cao,[2] Chiara Rafanelli,[3] Boheng Zhu,[4] Sara Gostoli[3]

Author affiliations

[1]Department of Healthcare, Affiliated Changzhou Maternity and Child Healthcare Hospital, Nanjing Medical University, Changzhou, China.

[2]Department of Gastroenterology, The Third Affiliated Hospital, Soochow University, Changzhou, China

[3]Department of Psychology "Renzo Canestrari", University of Bologna, Bologna, Italy

[4]Department of Psychological Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Correspondence to

Jianxin Cao; drtsao123@sina.cn.

Efficacy of group biofeedback treatment on Hyperemesis Gravidarum with psychosomatic symptoms diagnosed with the revised version of Diagnostic Criteria for Psychosomatic Research (DCPR-R): study protocol for a randomized controlled trial

Introduction

Hyperemesis Gravidarum (HG) is a condition characterized by dehydration, electrolyte imbalance, lack of nutrition, and at least 5% loss in body weight, occurring in the first half of pregnancy. The aim of this trial is to examine the efficacy of group biofeedback treatment on HG patients with psychosomatic symptoms, which will be evaluated through the revised version of Diagnostic Criteria for Psychosomatic Research (DCPR-R).

Methods and analysis

In this single-blinded randomized controlled clinical trial, sixty-eight HG patients diagnosed with at least one psychosomatic syndrome according to DCPR-R and aged 18-40 years, will be recruited in a Chinese Maternal and Child Health Hospital. The sample will be randomized (1:1) into two arms: experimental group, which will undergo to group biofeedback treatment, psycho-education and treatment as usual (TAU); and control group, which will undergo psycho-education and TAU only. The primary outcomes will be reduction of the frequency of psychosomatic syndromes, severity of nausea/vomiting, quality of life and heart rate variability. The secondary outcomes will include days of hospitalization, repeated hospitalization and laboratory investigations.

Ethics and dissemination

This study has received ethic approval from the Nanjing Medical University (NO. 2019/491, granted 22 February 2019). All participants will be required to provide written informed consent. Study outcomes will be disseminated through peer-reviewed publications and academic conferences, and used to confirm a tailored biofeedback intervention for HG patients with psychosomatic symptoms.

Trial registration number

Chinese Clinical Trial Registry Number: ChiCTR2000028754. Registered on 1 January 2020.

Strengths and limitations of this study

► This is the first study to evaluate psychosomatic syndromes in HG patients according to the revised version of the Diagnostic Criteria for Psychosomatic Research (DCPR-R).

► This study will investigate the effect of a group biofeedback therapy on the severity of nausea/vomiting among HG patients.

► This study will examine the effect of a group biofeedback therapy on the reduction of the frequency of psychosomatic syndromes evaluated by means of DCPR-R among HG patients.

► Since this is a single-blind trial, the placebo effect of biofeedback in the experimental group could not be excluded.

► The severity of psychosomatic symptoms will not be assessed, since DCPR-R syndromes are conceived as categorical constructs.

BACKGROUND

Hyperemesis Gravidarum (HG) is a condition characterized by dehydration, electrolyte imbalance, lack of nutrition, and at least 5% loss in body weight.[1] HG rates in pregnant women range from 0.3% to 3%, and it is considered one of the most important pregnancy-related complications.[2] HG appears in the first half and can last throughout the pregnancy, although the symptoms usually resolve within 20 gestational weeks.[2] Moreover, HG usually recurs in subsequent pregnancies following an affected one in up to the 81% of the cases.[3] This condition generally requires frequent visits to the emergency room and repeated hospitalizations for intravenous hydration, which severely compromise quality of life (QoL).[4] Hospitalization rates for HG vary between populations, such as from 1% to 2% in the United States[5] and 10.8% in Shanghai (China),[6] whereas about the 37.6% of women admitted to hospital for HG return for a second hospitalization during their pregnancy in Israel.[7]

The etiology and pathogenesis of HG remain uncertain, even though they are likely to be multi-factorial, including biological, psychological and socio-economic antecedents,[8] such as maternal endocrine disorders, hepatic abnormalities, gastrointestinal dysfunction, pituitary axis malfunction, autonomic nervous dysfunction, and psychosomatic factors.[9] The complications of HG include multiple nutritional deficiencies, Wernicke's encephalopathy, esophageal laceration, premature termination of the desired pregnancy and fear of subsequent pregnancy, preterm birth and low birth weight.[2]

The Diagnostic Criteria for Psychosomatic Research (DCPR) were developed to diagnose psychological disorders that could have a negative prognostic role in medical illnesses, but are not detectable with the use of Diagnostic and Statistical Manual of Mental Disorders (DSM) – based on traditional psychiatric criteria.[10] The DCPR have demonstrated an excellent predictive validity for psychosocial functioning and treatment outcomes in several medical settings, including oncology,[11] dermatology,[12] endocrinology,[13] cardiology,[14, 15] gastroenterology,[16] and immune system.[17] In 2017, a revised version of the DCPR (DCPR-R) was published.[18] To date, no study has examined the prevalence of the DCPR syndromes in HG.

Group biofeedback is a method to process in-vivo information related to psychological and physiological activities, such as muscle tension, skin temperature, heart rate, blood

pressure, brain waves, for multiple patients (2-20) at the same time.[19] Its working principles include heart rate variability biofeedback (HRVB), abdominal breathing and Jacobson's muscle relaxation.[20] Biofeedback constitutes a noninvasive psychological intervention, which showed its efficacy in the treatment of asthma, chronic obstructive pulmonary disease, irritable bowel syndrome, cyclic vomiting, recurrent abdominal pain, fibromyalgia, cardiac rehabilitation, hypertension, chronic muscle pain, pregnancy induced hypertension, depression, anxiety, post-traumatic stress disorder.[21] It was also used to decrease perinatal anxiety and depression in the third trimester[22] and psychological stress during the early postpartum period.[23] To our knowledge, there is no information about the efficacy of group biofeedback on psychosomatic symptoms in the first and early second trimester of pregnancy.[24]

We propose two hypotheses in this study. First, we hypothesize that the 2-week group biofeedback therapy will reduce the frequency of psychosomatic syndromes, the severity of nausea/vomiting, and improve the HRV index and quality of life of HG patients with psychosomatic syndromes. Second, with the remission of nausea or vomiting, we hypothesize that the days of hospital admission and the number of repeated HG treatments in the experimental group will be significantly smaller, and laboratory investigations significantly better, than those reported in the control group.

METHODS

Study design

This randomized controlled trial will be single-blind, in the sense that the investigators who will perform randomization, assessment and statistical analyses, will be blind to participants' group allocation. Change in primary outcome will be measured from baseline to 2-week post intervention, while change in secondary outcomes will be measured from baseline to 20weeks follow-up. All personal data will be treated confidentially. Protocol Version 1.1, dated 1 March 2017.

Participants

Patients will be recruited at the Department of Gynecology of Changzhou Maternity and

Child Healthcare Hospital affiliated with Nanjing Medical University, Changzhou, China. Approximately 190 HG patients were hospitalized yearly at this department. We expect to recruit 68 patients diagnosed with at least one psychosomatic syndrome.

A socio-demographic interview, including information on age, previous miscarriage, gestational age when vomiting started (weeks), days of vomiting at admission, hyperemesis in a previous pregnancy, income, level of education, employment status, medical history, weight at admission, will be administered at baseline.

Eligibility criteria

1. Diagnosis of HG in a singleton pregnancy documented by the presence of severe vomiting (more than 3 times per day without any other obvious cause), an inability to maintain oral nutrition, weight loss of more than 3 kilograms and at least one positive ketonuria test. [2]
2. At least one psychosomatic syndrome according to the evaluation of DCPR-R system.[18]
3. No evidence of antenatal bleeding, no antibiotic treatment, H2 blockers or proton pump inhibitors in the previous month.[25]
4. Patients without any psychiatric comorbidity (schizophrenia, bipolar disorder, substance dependence, personality disorder), as ascertained from the clinical records consultation.
5. Age ranging from 18 years to 40 years old.

Exclusion criteria

Exclusion criteria include fetal anomaly, antenatal bleeding, multiple pregnancy, systemic disease, hyperthyroidism, hepatic disorders, urinary tract infections or intracranial disorders, gastrointestinal diseases, and difficulty to understand the questions and follow the instruction.

Randomization and blinding

Participants who will be eligible in the screening phase and agree to sign the consent form, will be randomly assigned to the experimental group or control group. The random sequence numbering will be carried out by a computer program (the Random Allocation Software 2.0), with an allocation ratio of 1:1. An independent researcher, who will not join other procedures, will perform the randomization process in order to avoid bias.

The researcher responsible for the assessment will be blinded to participants' group allocation. The patients will be informed that two different intervention techniques will be tested. The interventions will be scheduled in different times and days, so that participants will not have contact between groups. Data collection will be conducted by a blinded and trained researcher.

Finally, the researcher responsible for statistical analyses will be blinded too. Once the study will be concluded, this researcher will receive a dataset with all necessary data without identification of participants and groups.

Intervention

Three interventions that will be performed in the two groups: group biofeedback intervention, psycho-education and treatment as usual (TAU). A nurse who received professional biofeedback training will administer the group biofeedback. The goal of this program is to help participants to learn diaphragmatic breathing techniques, Jacobson's muscle relaxation and guided Imagery, while monitoring heart rate variability (HRV). The intervention will include ten sessions delivered every working day in two weeks. Each session will last about 30-40 minutes, in a group setting (2-4 participants).

- Session 1. First, teach patients about the mechanism of group biofeedback, the science behind the technique, and potential benefits and outcomes of its use. Second, measure baseline HRV in 5-minute time interval. Third, teach participants the slow breathing at resonance frequency about 6.5 to 6 breaths/minute, for ten minutes. Finally, guide participants how to tense and relax larger groups of muscles: (a) feet and legs; (b) stomach and chest; (c) arms and hands; (d) shoulders, back, and neck; and (e) face. Muscle relaxation will last ten minutes.
- Session 2. First, measure the HRV in 5-minute time interval. Second, conduct the slow breathing at resonance frequency about 6 breaths/minute, for ten minutes. Finally, implement the progressive muscle relaxation and body scanning to manage tension for ten minutes.
- Session 3-5. Tell the participants to do as the session 2. In addition, participants are instructed to practice resonance frequency breathing as a 10-minute daily homework.
- Session 6-9. Tell the participants to do as sessions 3-5. Additionally, after muscle

relaxation, ask the participants to watch love, compassion, and forgiveness images on the computer screen, and encourage them to enter a calm, safe, content, and relaxed state through the guided imagery. This costs 10 minutes.

- Session 10. First, measure the HRV in 5-minute time interval as the post-intervention. Second, ask patients to think about three questions: "what have you experienced during the intervention", "what you have learned from the intervention", "which feedback exercise you will practice by yourself in the future". Tell patients they can do the exercises routinely, or when they just realize that they are overly emotional or dysfunctional. Finally, repeat the three exercises for the last time.

The psycho-education includes explanations of the detrimental effect of psychosomatic symptoms on the treatment of HG, of maternal anxiety and depression on both the fetus and the infant (i.e., behavioral problems, learning difficulties, psychiatric illness in the offspring, and premature termination of pregnancy). In addition, participants will also be told that and social interactions can help release anxiety and depression. Individual psychoeducation will be implemented only once for 30 minutes before each participant will be assigned either to experimental group or control group.

TAU will involve any recommendation given to the participants by their gynecologist, including parenteral antiemetic medications, electrolyte repletion, and nutritional support. Patients in both groups will be asked to follow gynecologists' recommendations, and are discharged once they are rehydrated and capable of maintaining adequate oral intake, which depend on the judgement of the gynecologist.

All the three interventions will be performed in the experimental group. Before patients will be involve in the group, they will receive the psychoeducation once for 30 minutes, then 10 sessions of group biofeedback and TAU, for two weeks. If patients will be discharged within the two weeks, they will be asked to come back to hospital every working day to complete the rest of the treatment.

In the control group, patients will receive the psycho-education once for 30 minutes before they will be allocated in the group, and then TAU only. They can be discharged once they will be rehydrated and capable of maintaining adequate oral intake. They will be asked to measure HRV once again after 2 weeks, whether discharged or hospitalized.

Primary outcomes

Literature showed that reduction of psychosomatic syndromes, as well as improvement of severity of nausea/vomiting, HRV and quality of life, might represent relevant outcomes to determine the efficacy of a specific intervention focused on HG.[4, 7] Moreover, the inclusion of both categorical (i.e., DCPR-R syndromes) and continuous (i.e., nausea/vomiting severity, HRV index and quality of life) variables as primary outcomes, could greatly support the efficacy of the treatment, in the event that improvements of both kinds of variables would be detected.

Psychosomatic syndromes

A revised version of the Semi-Structured Interview based on Diagnostic Criteria for Psychosomatic Research-Revised (DCPR-R) [18] will be used to assess the presence of psychosomatic syndromes. DCPR-R have a modular structure including 4 domains (i.e. stress, illness behavior, psychological manifestation, personality), and allow the formulation of 14 diagnostic rubrics: allostatic overload, health anxiety, disease phobia, hypochondriasis, thanatophobia, illness denial, persistent somatization, alexithymia, conversion symptoms, anniversary reaction, somatic symptoms secondary to a psychiatric disorder, demoralization, demoralization with hopelessness, irritable mood, type A behavior, and alexithymia. The interview has 79 yes/no items and focuses on the past 12 months. The updated version of DCPR[18] was developed based on insights derived from their use in a large number of samples and settings[17] and it includes the diagnostic criteria for two additional syndromes, allostatic overload and hypochondriasis. Both allostatic overload and hypochondriasis can be assessed by specific clinimetric criteria[26, 27] that underwent validation.[27-29] The use of DCPR was reported to be useful and reliable in the assessment and description of psychosomatic distress in general, medical and psychiatric populations, showing excellent interrater reliability, construct validity and predictive validity for psychosocial functioning and treatment outcome.[30-32] Skip instructions are provided and some questions do not need to be asked. Some items can be completed based on the interviewer's observation and clinical judgement without specific questioning. If participants will be discharged in less than two weeks, they will be reached by telephone to undergo the interview.

Severity of nausea/vomiting

The modified Pregnancy-Unique Quantification of Emesis and Nausea (modified-PUQE),[33] a 3-item self-rating scale that incorporates three dimensions (i.e. nausea, vomiting, retching), will be used to assess the severity of nausea /vomiting. It represents a valid index for the assessment of nausea/vomiting severity and its use is justified to assess global nausea/vomiting severity in the first trimester of pregnancy. The respondents are asked to indicate - on a 5-point Likert scale - the extent to which they agree with each statement. The sum score may range from 3-15. 3-6 represents mild nausea/vomiting; 7-12, moderate nausea/vomiting; and 13-15, severe nausea/ vomiting. The infraclass correlation coefficient was 0.71, and the severity of nausea/vomiting that was measured by the modified-PUQE was associated with QoL.[33]

HRV index

The biofeedback system (Heartmath, VISHEE, Nanjing) is used to monitor and record the HRV index, including the standard deviation of normal--to-normal intervals (SDNN) between adjacent heartbeats, high frequency (HF) and low frequency (LF)[34] HRV, and the ratio between LF and HF (LF/HF). SDNN represents the amount of variability in heartbeat intervals for a given time period; in this study 5-minute time intervals at pre-intervention and post-intervention are used.[35] The higher values of SDNN, the better health outcomes. HF HRV reflects parasympathetic activity and typically corresponds to the range between 0.15 and 0.40 Hz.[36, 37] LF HRV is influenced by both the sympathetic and parasympathetic systems, baroreflex activity and typically corresponds to the range between 0.05 and 0.15 Hz.

Quality of life (QoL)

Short-Form Health Survey with the standard 12-item version (SF-12)[38] will be used to measure QoL. This shorter version of the commonly used SF-36 yields 2 summary measures of physical and mental health. Summary measures will be calculated by adding the scores of the 12 items, with a range from 0-100; higher scores represent better QoL. The relative validity ranged from 0.43-0.93 (median 0.68) for physical health, and 0.60-1.07 (median 0.84) for the mental health.[38]

Secondary outcomes

Days of hospitalization

Length of hospitalization after enrollment, as recorded the patients' hospitalization days between pre-intervention and the discharge from the hospital. Patients are discharged once they are rehydrated and capable of maintaining adequate oral intake, upon the decision of their gynecologists. The longer length of hospital stays, the higher the economic costs are.

Re-hospitalization for HG

The repeated hospitalization for HG after the intervention until 20-week gestation, as measured follow-up after their first discharge from the hospital. All the participants will be asked by telephone whether they have received the HG treatment again after discharge, up to 20-week gestation.

Laboratory investigations

Ketonuria, renal function, serum electrolytes and full blood count results represent measures of severity of HG during hospitalization. All the participants will undergo the laboratory investigations at T0 and T1.

Monitoring

On the basis of the no risk of harms associated with the non-pharmaceutical intervention in this Clinical Trials of an Investigational Medicinal Product (CTIMP) trial, no interim analysis or data monitoring committee is planned.

Confidentiality

All data will be anonymized to ensure patient confidentiality is protected. A unique research number will be used to identify the participants' data in the database. Data will be kept securely and only the investigators have access to the data.

Evaluations

The participants in both groups will be evaluated with the SSI based on DCPR-R, SCID for DSM 5, modified-PUQE, HRV index, QoL and laboratory investigations before the treatment (T0), at the end of the treatment (i.e., two weeks later) (T1). Days of hospitalization and number of repeated hospitalization will be assessed as well at T2.

Participant timeline

Participants are identified in the Department of Gynecology according to eligibility criteria and exclusion criteria by research staff. Following gaining written consent, participants are immediately randomized to the control group or the intervention group. For those patients randomized to the control group, psychoeducation and TAU will be administered. For the intervention group, patients will receive 2-week biofeedback intervention additionally. The assessment of DCPR-R, modified-PUQE, HRV, QoL, and laboratory investigations will conduct before and after 2-week treatment, days of hospitalization and re-hospitalization for HG will be collected until 20-gestation week for both groups.

Sample size

Based on a previous trial about psychotherapy on nausea and vomiting of pregnant women, the SD of modified-PUQE in nausea and vomiting pregnant women is 3. [39] To detect a medium effect size (f=.25) at the statistical power of .90 based on a two sided significance level .05, a minimum sample of 44 participants will be required. Given an attrition rate of 35%, as observed in other biofeedback intervention trials, [40] it is expected to recruit at least 68 patients. G*Power3.1 has been used to calculate the sample size.

Patient and Public Involvement

Gynecology doctors from the Department of Gynecology of Changzhou Maternity and Child Healthcare Hospital were consulted in the development of the trial and reviewed the protocol. They provided valuable insights which led to considerations of ethical issues as well as feasibility, which resulted in the changes in inclusion criteria, outcome measures and continued treatment after the end of intervention. They introduced the project to their patients who will decide for themselves to participate in the research or not. The intervention fee of the experimental group would be paid by the two funding. We plan to inform the trial participants of the final results if requested.

Data access

Full access to the dataset will be held by the principal investigators, coinvestigators and statistician only.

Statistical analysis

All the data will be analyzed with the Statistical Package for Social Science 22.0 (SPSS 22.0). Repeated Measures ANOVA will be implemented to evaluate between and within groups changes in modified-PUQE, HRV index, QoL (primary outcome), and the laboratory investigations (secondary outcome). The reduction of the frequency of DCPR-R syndromes will be analyzed by means of logistic regression. Independent sample t test will be used to analyze differences concerning length of hospitalization (measured in days) and number of repeated hospitalization between two groups. Pearson Chi-squared tests and independent samples t tests will be performed to assess statistical differences on clinical and socio-demographic characteristics between two groups. In addition, Pearson Chi-squared tests will be used to assess the rate of moderate and severe nausea/vomiting in both groups pre and post intervention, respectively. Missing data will be dealt by means of multiple imputation procedures. The differences will be considered significant with a p value ≤ 0.05.

Ethics and dissemination

This study has received ethic approval from the Nanjing Medical University (NO. 2019/491, granted 22 February 2019) and it has been registered in the Chinese Clinical Trial Registry (Number: ChiCTR2000028754). All the data will be uploaded online to ResMan raw data sharing platform of China Clinical Trial Registry. All participants will be required to provide written informed consent (see Supplemental Material 1). Study outcomes will be disseminated through peer-reviewed publications and academic conferences, and they will be used to pave the ground to a tailored biofeedback intervention for HG patients with psychosomatic syndromes.

DISCUSSION

The DSM-5 has been regarded as the gold standard of psychiatric evaluation.[41] Anxiety and depression were common in the first trimester among HG women assessed during their first

hospitalization, with caseness rates of 20.6%~46.9% and 29.2%~47.8% respectively,[42] 36.3% and 22.1% from a longitudinal study of Chinese women in Hong Kong.[43]

However, the methodological flaws in studies have left the concept that anxiety and depression as a cause or outcome of HG unsupported by evidence,[44] and psychiatric diagnoses are not highly represented among women with HG who feel less overall healthy during the pregnancy.[45] First, the bulk of the existing data does suggest that even if women with HG feel less generally healthy during the pregnancy, psychiatric diagnoses are not over-represented longitudinally.[45] Most of the previous studies[46] used self-reporting scales (Beck Anxiety Inventory, Beck Depression Inventory, Hospital Anxiety and Depression Scale, Edinburgh Postnatal Depression Scale, Spielberger Anxiety Index) to screen and diagnose anxiety and depression, without structured psychiatric interview and observer-rated evaluation. Second, in the psychiatric medicine literature, demoralization during a medical illness is often misdiagnosed with depression[45]. Even though some symptoms can overlap with depression, patients with demoralization will have significant mood improvement when their medical circumstances improve, and this characteristic seems particularly applicable to women with HG and should diagnostically be considered first and foremost.[45] Third, psychosomatic aspects of HG has been proposed since 1984[47], but there is still no appropriate assessment tool performed in the clinical practice with these patients.

Compared with DSM-5, DCPR have been regarded as a more sensitive tool in detecting psychosomatic suffering,[48, 49] and showed their clinical utility in subtyping medical patients, identifying subthreshold or undetected syndromes, evaluating the burden of somatic syndromes, predicting treatment outcomes, and identifying risk factors.[17]

It is possible that in some women, vomiting becomes a conditioned or anticipatory response and – for this reason - it would be amenable to interventions such as psychotherapeutic approaches.[50] Literature showed positive results obtained with hypnotherapy[51] in treating nausea/vomiting in HG women. However, these findings were obtained from case series and did not include control groups, which makes difficult to differentiate true treatment benefits from normal recovery. Additionally, some patients could experience contradictory arousal effects deriving from some relaxation exercises in psychotherapy, which could make them more nervous and anxious.[52, 53]Therefore, in this

study, group biofeedback is selected as an intervention that allows patients to monitor their own emotional state in real time, during the treatment.

Biofeedback has been used to reduce perinatal anxious and depressive symptoms, and its safety for pregnant women is beyond doubt.[23] The three working principles (i.e., HRV, Jacobson's muscle relaxation and guided imagery) have been applied to improve physiological and psychological functions[54]. HRV, a key marker of parasympathetic functioning and a potent predictor of physical morbidity and mortality,[55] involves learning how to breathe at a resonance frequency rate, typically about 6 breaths per minute. Autonomic nervous dysfunction is also considered to be one of the possible etiology for HG. [9]HRV biofeedback training increases baro-reflexes and helps people develop healthier breathing patterns, and it permits the upregulation of the body ability to balance environmental change and physiological needs by improving baroreceptor and parasympathetic function [40]. Jacobson's progressive muscle relaxation (PMR) constitutes a systematic technique for achieving a deep state of relaxation through a progressive tensing and relaxation of various muscle groups. Application of PMR has been shown to reduce stress and anxiety, to improve symptoms such as tension headaches and insomnia, and to make a positive contribution to adjuvant therapy in cancer, chronic pain management in inflammatory arthritis, and irritable bowel syndrome.[56] Finally, guided imagery represents a tool to encourage subjects to enter a safe, calm, content, and relaxed state. A positive imagery activity is verbally introduced by the computer as a narration of thoughts and suggestions that guide the listener's imagination. Psycho-neuro-immunological theories propose that the psychological response to guided imagery may downregulate the hypothalamic-pituitary-adrenal axis, resulting in a reduced stress response, increased immune function, and greater sense of well-being.[57]

Compared with the control group, participants in the experimental group are expected to experience a significant decrease in the severity of nausea and vomiting, improvement of HRV index and laboratory results, better quality of life, shorter hospitalization stays, and lower frequency re-hospitalization for HG after the intervention. Findings from this study would contribute to a sensitive diagnostic criteria of psychosomatic symptoms for HG patients, and the development of a tailored protocol of group biofeedback intervention to

improve HG-related symptoms among both inpatients and outpatients with psychosomatic syndromes.

Two limitations of the study should be acknowledged. First, since this study will be a single-blind trial, patients will know whether they undergo to biofeedback therapy and, therefore, the placebo effect of biofeedback in the experimental group could not be excluded. Second, given that the DCPR-R syndromes are conceived as categorical constructs, we cannot ascertain the modification of symptoms severity following biofeedback therapy, but we will evaluate relief of DCPR-R syndromes after the 2-week therapy

Trial status

This study describes he first version of the protocol (V1.0). Patient recruitment is currently ongoing. If the protocol needs to be amended, the relevant parts of the study will be updated, and the changes will be recorded in the clinical trials registry (chictr.org.cn. ChiCTR2000028754). Due to the impact of COVID-19, our related researches have been severely affected, and will be appropriately postponed. The first patient has been enrolled on August 20,2020, and it is expected to finish by the end of 2022.

Abbreviations

DCPR-R: the revised version of Diagnostic Criteria for Psychosomatic Research; HG: Hyperemesis Gravidarum; TAU: treatment as usual; QoL: quality of life; DSM: Diagnostic and Statistical Manual of Mental Disorders; HRVB: heart rate variability biofeedback; modified-PUQE: modified Pregnancy-Unique Quantification of Emesis and Nausea; SDNN: standard deviation of normal--to-normal intervals; SF-12: Short-Form Health Survey with the standard 12-item version; CTIMP: Clinical Trials of an Investigational Medicinal Product;

Acknowledgements

The authors would like to thank patients and their doctors in the obstetrics and gynecology department at Changzhou Maternity and Child Healthcare Hospital Affiliated with Nanjing Medical University for making the study possible.

Authors' contributions

XC conceived the study and is the chief and principal investigator. XC and BZ designed the study. XC and SG wrote the protocol. JC and CR reviewed the manuscript. All authors read and approved the final manuscript.

Funding

The study did not receive funding for development. The PI is supported by the Jiangsu Natural Science Foundation (BK20190163) and China Postdoctoral Science Foundation (NO.243555). The organization that supports the PI did not and will not play a role in the study design, the collection, management, analysis and interpretation of the data.

Availability of data and materials

The datasets are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval

Prior to commencing the study, this study has been evaluated and approved by the Reasearch Ethical Board of the Nanjing Medical University (NO. 2019/491, granted 22 February 2019) in China.

Reference

1 King TL, Murphy PA: Evidence-based approaches to managing nausea and vomiting in early pregnancy. *J Midwifery Womens Health* 2009; 54:430-44.

2 Gynecology ACoOa: ACOG (American College of Obstetrics and Gynecology) Practice Bulletin: nausea and vomiting of pregnancy. *Obstet Gynecol* 2004; 103:803-14.

3 Dean CR, Bruin CM, O'Hara ME *et al*: The chance of recurrence of hyperemesis gravidarum: A systematic review. *Eur J Obstet Gynecol Reprod Biol X* 2019; 5:100105.

4 Eliakim R, Abulafia O, Sherer DM: Hyperemesis gravidarum: a current review. *Am J Perinatol* 2000; 17:207-18.

5 Jarnfelt-Samsioe A: Nausea and vomiting in pregnancy: a review. *Obstet Gynecol Surv* 1987; 42:422-7.

6 Zhang J, Cai WW: Severe vomiting during pregnancy: antenatal correlates and fetal outcomes. *Epidemiology* 1991; 2:454-7.

7 Morris ZH, Azab AN, Harlev S *et al*: Developing and validating a prognostic index predicting re-hospitalization of patients with Hyperemesis Gravidarum. *Eur J Obstet Gynecol Reprod Biol* 2018; 225:113-17.

8 Verberg MF, Gillott DJ, Al-Fardan N *et al*: Hyperemesis gravidarum, a literature review. *Hum Reprod Update* 2005; 11:527-39.

9 Bailit JL: Hyperemesis gravidarium: Epidemiologic findings from a large cohort. *Am J Obstet Gynecol* 2005; 193:811-4.

10 Fava GA, Freyberger HJ, Bech P *et al*: Diagnostic criteria for use in psychosomatic research. *Psychother Psychosom* 1995; 63:1-8.

11 Grassi L, Sabato S, Rossi E *et al*: Use of the diagnostic criteria for psychosomatic research in oncology. *Psychother Psychosom* 2005; 74:100-7.

12 Picardi A, Porcelli P, Pasquini P *et al*: Integration of multiple criteria for psychosomatic assessment of dermatological patients. *Psychosomatics* 2006; 47:122-8.

13 Sonino N, Peruzzi P: A psychoneuroendocrinology service. *Psychother Psychosom* 2009; 78:346-51.

14 Rafanelli C, Roncuzzi R, Milaneschi Y *et al*: Stressful life events, depression and demoralization as risk factors for acute coronary heart disease. *Psychother Psychosom* 2005; 74:179-84.

15 Rafanelli C, Sirri L, Grandi S *et al*: Is depression the wrong treatment target for improving outcome in coronary artery disease? *Psychother Psychosom* 2013; 82:285-91.

16 Cao J, Ding L: Psychosomatic Practice in Gastroenterology: New Insights and Models from China. *Psychother Psychosom* 2019; 88:321-26.

17 Porcelli P, Guidi J: The Clinical Utility of the Diagnostic Criteria for Psychosomatic Research: A Review of Studies. *Psychother Psychosom* 2015; 84:265-72.

18 Fava GA, Cosci F, Sonino N: Current Psychosomatic Practice. *Psychother Psychosom* 2017; 86:13-30.

19 Fisher CJ, Moravec CS, Khorshid L: The "How and Why" of Group Biofeedback for Chronic Disease Management. *Appl Psychophysiol Biofeedback* 2018; 43:333-40.

20 Aritzeta A, Soroa G, Balluerka N *et al*: Reducing Anxiety and Improving Academic Performance Through a Biofeedback Relaxation Training Program. *Appl Psychophysiol Biofeedback* 2017; 42:193-202.

21 Lehrer PM, Gevirtz R: Heart rate variability biofeedback: how and why does it work? *Front Psychol* 2014; 5:756.

22 Beckham AJ, Greene TB, Meltzer-Brody S: A pilot study of heart rate variability biofeedback therapy in the treatment of perinatal depression on a specialized perinatal psychiatry inpatient unit. *Arch Womens Ment Health* 2013; 16:59-65.

23 Kudo N, Shinohara H, Kodama H: Heart rate variability biofeedback intervention for reduction of psychological stress during the early postpartum period. *Appl Psychophysiol Biofeedback* 2014; 39:203-11.

24 Pinter A, Szatmari S, Jr., Horvath T *et al*: Cardiac dysautonomia in depression - heart rate variability biofeedback as a potential add-on therapy. *Neuropsychiatr Dis Treat* 2019; 15:1287-310.

25 Annagur BB, Tazegul A, Gunduz S: Do psychiatric disorders continue during pregnancy in women with hyperemesis gravidarum: a prospective study. *Gen Hosp Psychiatry* 2013; 35:492-6.

26 Giovanni A Fava , Jenny Guidi, Federica Semprini *et al*: Clinical assessment of allostatic load and clinimetric criteria. *Psychother Psychosom* 2010; 79:280-84.

27 Fiammetta Cosci , Fava GA: The clinical inadequacy of the DSM-5 classification of somatic symptom and related disorders: an alternative trans-diagnostic model. *CNS Spectr* 2016; 21:310-17.

28 Emanuela Offidani, Chiara Rafanelli, Sara Gostoli *et al*: Allostatic overload in patients with atrial fibrillation. *Int J Cardiol* 2013; 165:375-76.

29 Giovanni A Fava , Bruce S McEwen , Jenny Guidi *et al*: Clinical characterization of allostatic overload. *Psychoneuroendocrinology* 2019; 108:94-101.

30 Galeazzi GM, Ferrari S, Mackinnon A *et al*: Interrater Reliability, Prevalence, and Relation to ICD-10 Diagnoses of the Diagnostic Criteria for Psychosomatic Research in Consultation-Liaison Psychiatry Patients. *Psychosomatics* 2004; 45:386-93.

31 Jenny Guidi , Antonio Piolanti , Carmen Berrocal *et al*: Incremental Validity Of The Diagnostic Criteria For Psychosomatic Research - Revised (DCPR-R) To Clinical Assessment In Primary Care. *Psychiatry Res* 2020; 291:113233.

32 Sara Gostoli, Maria Montecchiarini , Alessia Urgese *et al*: The clinical utility of a comprehensive psychosomatic assessment in the program for colorectal cancer prevention: a cross-sectional study. *Science Report* 2021; 11:15575.

33 Lacasse A, Rey E, Ferreira E *et al*: Validity of a modified Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) scoring index to assess severity of nausea and vomiting of pregnancy. *Am J Obstet Gynecol* 2008; 198:71 e1-7.

34 Sgoifo A, Carnevali L, Alfonso Mde L *et al*: Autonomic dysfunction and heart rate variability in depression. *Stress* 2015; 18:343-52.

35 Vaschillo EG, Vaschillo B, Lehrer PM: Characteristics of resonance in heart rate variability stimulated by biofeedback. *Appl Psychophysiol Biofeedback* 2006; 31:129-42.

36 Karavidas MK, Lehrer PM, Vaschillo E *et al*: Preliminary results of an open label study of heart rate variability biofeedback for the treatment of major depression. *Appl Psychophysiol Biofeedback* 2007; 32:19-30.

37 Kemp AH, Quintana DS, Felmingham KL *et al*: Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for

cardiovascular risk. *PLoS One* 2012; 7:e30777.

38 Ware J, Jr., Kosinski M, Keller SD: A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; 34:220-33.

39 Shakiba M, Parsi H, Shikhi ZP *et al*: The Effect of Psycho-Education Intervention Based on Relaxation Methods and Guided Imagery on Nausea and Vomiting of Pregnant Women. *Journal of Family and Reproductive Health* 2019; 13:47-55.

40 Caldwell YT, Steffen PR: Adding HRV biofeedback to psychotherapy increases heart rate variability and improves the treatment of major depressive disorder. *Int J Psychophysiol* 2018; 131:96-101.

41 A C, RS M: Mental disorders in primary care. A guide to their evaluation and management. Oxford: Oxford University Press; 2017.

42 Tan PC, Vani S, Lim BK *et al*: Anxiety and depression in hyperemesis gravidarum: prevalence, risk factors and correlation with clinical severity. *Eur J Obstet Gynecol Reprod Biol* 2010; 149:153-8.

43 Lee AM, Lam SK, Sze Mun Lau SM *et al*: Prevalence, course, and risk factors for antenatal anxiety and depression. *Obstet Gynecol* 2007; 110:1102-12.

44 Fejzo MS: Measures of depression and anxiety in women with hyperemesis gravidarum are flawed. *Evid Based Nurs* 2017; 20:78-79.

45 Kim DR, Connolly KR, Cristancho P *et al*: Psychiatric consultation of patients with hyperemesis gravidarum. *Arch Womens Ment Health* 2009; 12:61-7.

46 Mitchell-Jones N, Gallos I, Farren J *et al*: Psychological morbidity associated with hyperemesis gravidarum: a systematic review and meta-analysis. *Bjog* 2017; 124:20-30.

47 Ringler M, Krizmanits A: Psychosomatic aspects of emesis gravidarum: somatic and psychosocial status of females in early pregnancy. *Z Geburtshilfe Perinatol* 1984; 188:234-8.

48 Mangelli L, Bravi A, Fava GA *et al*: Assessing somatization with various diagnostic criteria. *Psychosomatics* 2009; 50:38-41.

49 Sirri L, Fava GA: Diagnostic criteria for psychosomatic research and somatic symptom disorders. *Int Rev Psychiatry* 2013; 25:19-30.

50 Madrid A, Giovannoli R, Wolfe M: Treating persistent nausea of pregnancy with hypnosis: four cases. *Am J Clin Hypn* 2011; 54:107-15.

51 Fuchs K, Paldi E, Abramovici H *et al*: Treatment of hyperemesis gravidarum by hypnosis. *Int J Clin Exp Hypn* 1980; 28:313-23.

52 Barlow DH: Anxiety and its disorders: The nature and treatment of anxiety and panic (2nd ed). New York: Guilford Press; 2002.

53 Clark DM: Cognitive-behavior therapy for psychiatric problems: A practical guide, vol. Oxford University Press. Oxford University Press: New York; 1989.

54 Mcgrady A: Effects of group relaxation training and thermal biofeedback on blood pressure and related physiological and psychological variables in essential hypertension. *Biofeedback and self-regulation* 1994; 19:51.

55 Kemp AH, S. QD, R. QC *et al*: Major depressive disorder with melancholia displays robust alterations in resting state heart rate and its variability: implications for future morbidity and mortality. *Frontiers in Psychology* 2014; 5:1387.

56 Innes KE, Selfe TK, Vishnu A: Mind-body therapies for menopausal symptoms: a systematic review. *Maturitas* 2010; 66:135-49.

57 Roffe L, Schmidt K, Ernst E: A systematic review of guided imagery as an adjuvant cancer therapy. *Psychooncology* 2005; 14:607-17.

知情同意书

尊敬的患者：

我们将邀请您参加一项临床研究。本知情同意书提供给您一些信息以帮助您决定是否参加此项临床研究。请您仔细阅读，如有任何疑问请向负责该项研究的研究者提出。

您参加本项研究是自愿的。本次研究已通过常州市妇幼保健院医学伦理委员会审查。

如果您愿意，请仔细阅读以下内容。

方案名称：团体生物反馈辅助治疗伴心身症状的妊娠剧吐
研究中心：常州市妇幼保健院
主要研究者：崔雪莲，王丽，顾建东。

一、研究目的

妊娠呕吐（HG）的特征是脱水，电解质失衡，缺乏营养以及体重减轻至少 5%。孕妇的 HG 率在 0.3%至 3%的范围内，被认为是最重要的妊娠相关并发症之一，始于孕早期，可持续整个妊娠期，尽管症状通常会在第 20 周消退。该病通常需要经常去急诊室就诊并反复住院以进行静脉补液，这严重破坏了生活质量。住院率因人群而异，在美国为 1%至 2%，但在中国上海据报道为 10.8%。 HG 的并发症包括多种营养缺乏症，甚至包括 Wernicke 脑病，食道裂伤，心理社会影响（终止妊娠，并担心随后怀孕），以及孕妇的有创复苏，早产和胎儿低出生体重。妊娠剧吐发病原因不明确，现研究认为是多因素疾病，其中自主神经功能紊乱和心理因素也是可能的原因。但是目前研究中用来评估心理因素的工具存在缺陷和不足，而且尚没有较好的干预伴心身症状的妊娠剧吐的方法。因此本研究拟探索非侵入性的团体生物反馈治疗对妊娠剧吐的恶心呕吐症状以及患者的生活治疗、经济负担是否有改善作用。

二、研究过程

如果您同意参与这项研究，我们将对您进行编号，建立病历档案。在研究过程中我们仅需要采集一些您的电生理数据，因为这不是向您身体输入任何东西，所以不会对胎儿造成影响。您将被电脑随机分配到试验组或对照组，每组接受的治疗方式不完全相同，具体治疗方法由入组之后的治疗师向您讲解。试验时间为期 2 周，试验结束后会有工作人员对您进行电话随访，询问您的妊娠情况。

三、风险与不适

对于您来说，所有的信息将是保密的。这项研究所采用的干预方法不会对胎儿造成任何风险。

四、受益

通过对您的数据检测将有助于对疾病的干预效果作出诊断，为您的治疗提供必要的建议，或为疾病的研究提供有益的信息。

五、责任

作为受试者，您有以下职责：提供有关自身病史和当前身体状况的真实情况；告诉研究医生自己在本次研究期间所出现的任何不适；不得服用受限制的药物、食物等；告诉研究医生自己在最近是否曾参与其他研究，或目前正参与其他研究。

六、隐私问题

如果您决定参加本项研究，您参加试验及在试验中的个人资料均属保密。可以识别您身份的信息将不会透露给研究小组以外的成员，除非获得您的许可。所有的研究成员和研究申办方都被要求对您的身份保密。您的档案将保存在有锁的档案柜中，仅供研究人员查阅。为确保研究按照规定进行，必要时，政府管理部门或伦理审查委员会的成员按规定可以在研究单位查阅您的个人资料。这项研究结果发表时，将不会披露您个人的任何资料。

除本研究以外，有可能在今后的其他研究中会再次利用您的医疗记录、血/尿/病理检查标本。您现在也可以声明拒绝除本研究外的其他研究利用您的医疗记录和病理标本。

七、权利

如果您因参与这项研究而受到伤害：如发生与该项临床研究相关的损害时，您可以获得免费治疗和/或相应的补偿。

您可以选择不参加本项研究，或者在任何时候通知研究者要求退出研究，您的数据将不纳入研究结果，您的任何医疗待遇与权益不会因此而受到影响。

如果您需要其它治疗，或者您没有遵守研究计划，或者发生了与研究相关的损伤或者有任何其它原因，研究医师可以终止您继续参与本项研究。

您可随时了解与本研究有关的信息资料和研究进展，如果您有与本研究有关的问题，或您在研究过程中发生了任何不适与损伤，或有关于本项研究参加者权益方面的问题您可以随时与研究者联系。

方案版本号及日期：　　知情同意书版本号及日期：

知情同意书

我已经阅读了本知情同意书。

我有机会提问而且所有问题均已得到解答。

我理解参加本项研究是自愿的。

我可以选择不参加本项研究，或者在任何时候通知研究者后退出而不会遭到歧视或报复，我的任何医疗待遇与权益不会因此而受到影响。

如果我需要其它治疗，或者我没有遵守研究计划，或者发生了与研究相关的损伤或者有任何其它原因，研究医师可以终止我继续参与本项研究。

我将收到一份签过字的知情同意书副本。

最后，我决定同意参加本项研究。

受试者签名：[illegible]　　签名日期：2021年5月10日

受试者联系电话：15106110662

我已准确地将这份文件告知受试者，他/她准确地阅读了这份知情同意书，并证明该受试者有机会提出问题。我证明他/她是自愿同意的。

研究者签名：崔雪洋　　签名日期：2021年5月10日

研究者联系电话：15361125185

Informed Consent

Dear participants,

We will invite you to participate in a clinical study. This informed consent gives you some information to help you decide whether to participate in this clinical study. Please read it carefully and ask the investigator responsible for the study if you have any questions.

Your participation in this research is voluntary. This study has been reviewed by the Medical Ethics Committee of Nanjing Medical University.

If you like, please read the following carefully.

Project name: Group Biofeedback for Treatment of Hyperemesis Gravidarum with Psychosomatic Symptoms

Research institute: Changzhou Maternity and Child Healthcare Hospital.

Principle investigator: Xuelian Cui, Li Wang, Jiandong Gu.

1. Aims

Hyperemesis Gravidarum (HG) is a condition characterized by dehydration, electrolyte imbalance, lack of nutrition, and at least 5% loss in body weight. HG rates in pregnant women range from 0.3% to 3%, and it is considered one of the most important pregnancy-related complications. HG appears in the first half and can last throughout the pregnancy, although the symptoms usually resolve within 20 gestational weeks. This condition generally requires frequent visits to the emergency room and repeated hospitalizations for intravenous hydration, which severely compromise quality of life (QoL). Hospitalization rates for HG vary between populations: from 1% to 2% in the United States, 10.8% in Shanghai, China. The complications of HG include multiple nutritional deficiencies, Wernicke's encephalopathy, esophageal laceration, terminate the desired pregnancy and fear of subsequent pregnancy, preterm birth and low birth weight. The etiology and pathogenesis of HG remain uncertain, but should be multi-factorial with biologic, psychological and socio-economic antecedents [6], including maternal endocrine disorders, hepatic abnormalities, gastrointestinal dysfunction, pituitary axis

malfunction, autonomic nervous dysfunction, and psychosomatic factors. However, the methodological flaws in studies have left the concept that anxiety and depression as a cause or outcome of HG unsupported by evidence, and there is no good way to intervene in Hyperemesis Gravidarum with psychosomatic symptoms. The present study aims to explore the efficacy of group biofeedback treatment on nausea/vomiting and quality of life of HG patients with psychosomatic symptoms.

2. Procedures

If you agree to participate in this study, we will number you and create a medical record file. During the research we only need to collect some of your electrophysiological data, because this is not input to your body, so it will not affect the fetus. You will be randomly assigned to the experimental group or the control group by the computer. Each group receives different treatment methods. The specific treatment method will be explained to you by the therapist in the group. The duration of the test is 2 weeks. After the test, a staff member will follow up with you on the phone to inquire about your pregnancy.

3. Risks

For you, all information will be kept confidential. The interventions used in this study pose no risk to the fetus and pregnant women.

4. Benefits

From testing your data in this study, it will help diagnose the efficacy of disease interventions, provide necessary advice for your treatment, and provide useful information for disease research.

5. Responsibilities

As a participant, you have the following responsibilities: provide truthful information about your medical history and current physical condition; tell the researcher about any discomforts that you have experienced during this study period; do not take restricted drugs, food, etc ; tell the researcher whether you have participated in other research recently, or is currently participating in other research.

6. Privacy

If you decide to participate in this study, your personal information in the trial and during the trial will be kept confidential. Information that can identify you will not be shared with members outside the research team unless you have obtained your permission. All research members and research sponsors are required to keep your identity confidentially. Your files will be kept in locked file cabinets for research personnel only. To ensure that research is carried out in accordance with regulations, members of government administrations or ethics review committees can access your personal data at the research unit as required. When this research is published, no personal information about you will be disclosed.

7. Rights

If you are harmed by participating in this study: If damage occurs in connection with the clinical study, you can get compensation.

You can choose not to participate in the study, or notify the researcher at any time to request to withdraw from the study, your data will not be included in the study results, and any of your medical treatment and rights will not be affected.

The research physician may terminate your continued participation in the study if you require additional treatment, or if you do not follow the study plan, or if there is any injury related to the study, or for any other reasons.

You can keep informed of the information and research progress related to this research at any time, if you have questions related to this research, or if you have any discomfort and injury during the research, or have questions about the rights of participants in this research, you can contact the researcher at any time.

方案版本号及日期： 知情同意书版本号及日期：

Informed Consent

I have read this informed consent.

I had the opportunity to ask and all questions were answered.

I understand that participation in this study is voluntary.

I can choose not to participate in this research, or to withdraw from the research at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

The researcher may terminate my participation in this study if I need additional treatment, or if I do not follow the research plan, or if there is any research-related injury or for any other reason.

I will receive a signed copy of the informed consent form.

Finally, I decide to participate in this study.

Participant signature: Song Liu Date: 2021 year 5 month 10 day

Telephone number: 15106110662

I have accurately informed the participant of this document, she has read this informed consent accurately and has demonstrated that the participant has an opportunity to ask any questions. I certify that she agreed voluntarily.

Researcher signature: Xuelian Lai Date: 2021 year 5 month 10 day

Telephone number: 15961125185

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1/2/2020
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	13

contributorship			
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/a No sponsor
Roles and responsibilities: sponsor and funder	#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	N/a No sponsor
Roles and responsibilities: committees	#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)	N/a No committees
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	2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
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, non-inferiority, exploratory)	5
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	5
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)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
Interventions: modifications	#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)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	8
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)	11
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions	11

		supporting any sample size calculations	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
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	6
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	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate	10

		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	
Data collection plan: retention	#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	10
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	10
Statistics: outcomes	#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	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#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)	11
Methods: Monitoring			
Data monitoring: formal committee	#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	10
Data monitoring:	#21b	Description of any interim analyses and stopping	10

interim analysis		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	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
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)	N/a The first version, no amendments
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/a no
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	10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11

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	N/a
Dissemination policy: trial results	#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	1
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	1
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	1
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	6
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	10

Word count 3427