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Internet-based cognitive behavioral therapy for prevention of depression during pregnancy and in the postpartum (iPDP): a protocol for a large scale randomized controlled trial

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Title: Internet-based cognitive behavioral therapy for prevention of depression during pregnancy and in the postpartum (iPDP): a protocol for a large scale randomized controlled trial

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Abstract

Introduction: The objective of this randomized controlled trial (RCT) is to examine the effects of smartphone-based cognitive behavioral therapy (CBT) in preventing the onset of major depressive episodes (MDE) among pregnant women.

Methods and analysis: The target study population will be pregnant women of 16 to 20 weeks gestation who are currently users of "Luna Luna Baby", the most widely used app for pregnant women in Japan. Those who meet the eligibility criteria will be randomly allocated to the 6-module internet cognitive behavioral therapy (iCBT) program that was newly developed for pregnant women (n=2500), or to a treatment-as-usual control group (n=2500). Participants in the intervention groups will be required to complete the program by 32 weeks gestation. The primary outcomes are the number of new onsets of MDE, measured by using the World Health Organization Composite International Diagnostic Interview 3.0 (WHO-CIDI 3.0) at 32 weeks gestation and 3 months postpartum.

Ethics and dissemination: The study plan has been approved by the Research Ethics Review Board of the Graduate School of Medicine/Faculty of Medicine, the University of Tokyo (2019150NI). If the intervention programs are found to produce a significant positive effect in this RCT, these programs can be made available for all users of the app in the future.

Key words: smartphone-based cognitive behavioral therapy, antenatal depression, postpartum depression, prevention

Trial registration number: UMIN000038190; Pre-results.

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Article Summary

Strengths and limitations of this study

- The large sample size of this RCT can lead to a definitive result of the effectiveness of the fully automated smartphone-based CBT program in preventing both antenatal and postpartum depression.
- The newly developed program designed to handle concerns extracted from pregnant women would be practical and expect low dropout.
- This study will also evaluate the implementation outcomes of the program, which will contribute to the dissemination and implementation of iCBT.
- This RCT will also clarify whether iCBT during pregnancy can prevent maternity blues.
- A limitation of this study is that all of the outcomes will be measured by self-report.

Introduction

Prevention of perinatal depression is a critical public health issue.[1] The prevalence of antenatal depression was reported to be 7.4% in the first trimester, 12.8% in the second trimester, and 12.0% in the third trimester;[2] and the prevalence of postpartum depression was estimated to be 17.7%, though there is significant heterogeneity across nations.[3] Antenatal depression is associated with failing to seek prenatal care, an inadequate diet and/or use of tobacco, alcohol, or other harmful substances, self-harm or attempted suicide, and postpartum depression; while postpartum depression is associated with negative outcomes such as physical and psychological abuse to their children, and infanticide.[4] Furthermore, perinatal depression can also affect development from fetus to adolescent and paternal depression.[5-10] Therefore, preventing perinatal depression in the antenatal period is crucially important.

Given the large number of pregnant women who have risk factors such as maternal anxiety, life stress, lack of social support, unintended pregnancy, domestic violence, lower income and education, and poor relationships, making it difficult to identify and screen all high-risk pregnant women,[11] universal prevention should be more valued. According to a systematic review and meta-analysis, psychological interventions have been recommended as the most effective approach to prevent antenatal and postpartum depression.[12] Cognitive behavioral therapy (CBT) has been broadly researched and reported to be highly effective among psychological interventions.[13,14] Previous meta-analyses showed that the effect size of psychological intervention as universal prevention for postpartum depression was reported to be 0.19[15] and 0.37.[13] The timing of interventions of RCTs included in these meta-analyses were both during pregnancy and postpartum.

With respect to universal prevention, fully automated internet-based CBT (iCBT) is desirable to face-to-face or guided iCBT in terms of accessibility, anonymity, and cost-effectiveness.[16] Although a systematic review showed a positive effect of iCBT for the improvement of perinatal depressive symptoms,[17] to our knowledge, there have been only two randomized controlled trials (RCTs) for universal prevention using automated iCBT during pregnancy.[18,19] These two studies

did not assess the major depressive episode (MDE); instead, they used depressive symptoms as outcomes. In addition, dropout from iCBT in these studies was relatively high (66% and 44%, respectively). A large number of sessions and/or the length per session may be impractical for a substantial number of pregnant women to complete, which may cause a high dropout rate. Thus, it would be necessary to develop a program that is more acceptable and feasible for pregnant women.

The objective of this randomized controlled trial (RCT) is to examine the effectiveness of the newly developed 6-sessions of 5 to 10-minutes, smartphone-based, automated iCBT programs in preventing the onset of MDE at the third trimester and 3-months postpartum among pregnant women currently in the second trimester. The program would be practical and could be utilized by many pregnant women. In addition, intervention during early pregnancy will enable the prevention of not only postpartum depression but also antenatal depression.

Methods and Analysis

Trial design

The study will be a two-arm, parallel-group, treatment-as-usual (TAU) controlled, randomized trial. The allocation ratio of the intervention groups to the control group is 1:1. Random assignments are stratified by K6 scores (groups of 4 points or less and groups of 5 points or more) in the baseline survey. End-users of an app ("Luna Luna Baby" run by MTI Ltd.) that provides useful information for pregnant women will be recruited. Follow-up assessments will be conducted at 32 weeks gestation and 3-months postpartum. This protocol is written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guideline checklist.[20] Trial start date was the 27th of November, 2019 and the last follow-up date will be the 31st of March, 2021.

Participants

Pregnant women who have user IDs for the latest version of the app and meet the following criteria will be invited to participate in this RCT.

Eligibility criteria

1. Being over 20 years old

2. Being 16 to 20 weeks gestation

3. Not diagnosed with a major depressive episode in the past month by the web-based self-administered version of the WHO Composite International Diagnostic Interview 3.0 (WHO-CIDI 3.0)[21]

4. Not diagnosed with lifetime bipolar disorder (WHO-CIDI 3.0)

5. Ability to understand the research objectives and give consent

Pregnant women using the app register the date of the last menstruation and the expected date of childbirth in the app. Thus we can find out the number of weeks of pregnancy.

Recruitment

Figure 1 shows the study flow of this trial. MTI Ltd. sends an invitation message to potentially eligible pregnant women, which will include an explanation of the study and information on the eligibility criteria. After reading the explanation of the study, potential participants will be invited to give their consent on the app to participate in the study, and to complete and return the baseline survey.

MTI Ltd. will also send messages to study participants to join in follow-up assessments.

Five thousand pregnant women will be randomized to either the intervention group (n=2500), or the control group (n=2500). Participants in the intervention groups will be required to complete the intervention program within 12 weeks after the baseline survey.

Participants in the intervention groups will be required to complete the CBT program up to 32 weeks gestation. Participants will be asked not to share this information through any social network. The participants will be reminded by a popup message to complete the program if they have not already done so. Intervention programs will be closed at 32 weeks gestation.

Participants in the control group will not receive any intervention programs during the intervention and follow-up period. General information about mental health during pregnancy will be provided to participants in both the intervention group and the control group as a TAU.

Interventions

A smartphone-based six-module CBT program designed for pregnant women was newly developed. This program will be provided via the Luna Luna Baby app, so users of the app don't have to download another app. Some components of the modules were derived from a previous iCBT program that successfully prevented the onset of MDE among office workers.[22] Other components such as behavioral activation based on values, self-compassion and mindfulness have been incorporated, which could be regarded as the third wave CBT. The six modules are presented in a fixed

order, with one module accessible per week, from module 1 to module 6. It will take about 5 min to complete each module. The program includes psychoeducation (module 1), case formulation based on a cognitive behavioral model (module 2), behavioral activation (module 3), self-compassion (module 4), mindfulness (module 5), and problem-solving (module 6). Details of each of the components are as follows.

Psychoeducation (module 1)

In this module, participants learn about the roles of what are generally called "negative" emotions such as anxiety, depressive mood and anger. Each emotion is necessary for us; for example, anxiety is a sign that warns us of some risk in the future, and promotes us to prepare for the future. This module was designed to help participants face and deal with their own emotions in subsequent modules.

Case formulation based on cognitive-behavioral model (module 2)

In this module, participants learn about a cognitive-behavioral (CB) model, especially the five-part model (situation, thoughts, emotions, behavior and physical sensations) and a case formulation based on this model.[23] Case formulation is a method used to understand the problems of patients or clients. Case formulation is helpful for participants to choose an appropriate approach to change the vicious circles of these five areas.

Behavioral activation (module 3)

Behavioral activation is a process to increase pleasurable and rewarding activities using

behavioral strategies such as activity scheduling. This module provides a behavioral activation technique for enhancing participants' liveliness. In this module, participants learn about the theory of behavioral activation and how to plan an activity schedule to increase pleasant activities. Participants are also encouraged to identify their values, based on brief behavioral activation therapy for depression (BATD),[24] and acceptance and commitment therapy (ACT).[25]

Self-compassion (module 4)

Self-compassion indicates a positive and caring attitude of a person towards herself in the face of stressful events.[26] As a result of this attitude, individuals who are highly self-compassionate are expected to experience higher individual well-being.[27] Three interrelated determine the self-compassionate reactions to negative events and experiences: self-kindness, sense of common humanity and mindfulness. In this module, participants learn the concept of self-compassion and how to express compassion towards themselves.

Mindfulness (module 5)

Mindfulness is defined as "paying attention in a particular way: on purpose, in the present moment, and nonjudgmentally".[28] Mindful persons are likely to be aware of the physical sensation, thoughts, and emotions at that moment, which enables them to stop their usual reactions to a stressful event so that symptoms and problematic behaviors are likely to disappear. In this module, participants learn about the concept of mindfulness and how to practice it through listening to voice guidance.

Problem-solving (module 6)

Problem-solving technique is a CB intervention that focuses on training adaptive problem-solving attitudes and skills.[29] A rational problem-solving style contains the systematic application of four problem-solving skills: (1) problem definition and formulation, (2) generation of alternative solutions, (3) decision making and (4) solution implementation and verification. In this module, participants learn about problem-solving skills to sort out the problem and make a list of solutions, and assertiveness to communicate with their partners confidently.

Outcomes

Table 2 shows an overview of the outcome measures. Those who have not responded by more than a week after the online questionnaire is distributed will receive a popup message to complete each assessment.

Primary outcome

The primary outcome is the onset of MDE during the 32 weeks gestation and 3 months postpartum. The onset of MDE during the follow-up will be assessed using the web-based self-administered version of the Japanese WHO-CIDI 3.0 depression section, according to DSM-IV-TR criteria. The web version has been shown to have a good concordance with the clinical diagnosis of MDE and to be reliable in a 1-year test-retest survey. An incident case with MDE will be identified if a respondent reports an episode of MDE at either 32 weeks gestation or 3 months postpartum. An onset month for an episode of MDE also will be requested. In addition, two other definitions are applied to

identify sub-threshold depressive episodes: one requires a shorter duration of symptoms (i.e. 7 days or more, rather than 2 weeks or more); the other one requires having a fewer symptoms (i.e. having 3 symptoms or more, instead of 5 symptoms or more).

Secondary outcomes

The Edinburgh Postnatal Depression Scale (EPDS)

EPDS is used most often for screening perinatal depression because it focuses on cognitive symptoms of depression and excludes somatic items that can generate false positives during pregnancy and postpartum. It consists of 10 items, with 0-3 points scored per item for a potential scale score of 0-30. The higher scores indicate more severe depressive symptoms. EPDS will be conducted at baseline, 32 weeks gestation, 1 week postpartum and 3 months postpartum.

Kessler's Psychological Distress Scale (K6)

Psychological distress is measured by the Japanese version of K6.[30,31] K6 consists of six items assessing the frequency with which respondents have experienced symptoms of psychological distress during the past 30 days. The response options range from 0 (none of the time) to 4 (all of the time), and the total score ranges from 0 to 24. The higher scores indicate more severe psychological distress. K6 will be conducted at baseline, 32 weeks gestation, 1 week postpartum and 3 months postpartum.

EuroQol -5 dimension-5 level (ED-5D-5L)

General health status will be measured by the EQ-5D-5L.[32-34] It is a 5-dimensional utility

instrument consisting of domains about morbidity, self-care, usual activities, pain or discomfort, and anxiety or depression. Each domain is divided into 5 levels of severity (none, slight, moderate, severe, extreme problems, or unable to). All responses are converted into a single index score of general health status. ED-5D-5L will be conducted at baseline, 32 weeks gestation and 3 months postpartum.

Somatic symptom Scale-8 (SSS-8)

Somatic symptoms will be measured by Japanese version of SSS-8.[35,36] SSS-8 consists of 8 items that assess the following symptoms: stomach or bowel problems; back pain; pain in the arms, legs, or joints; headaches; chest pain or shortness of breath; dizziness; feeling tired or having low energy; and trouble sleeping. These items comprise the four symptom domains of gastrointestinal, pain, cardiopulmonary, and fatigue. Respondents rate how much each symptom has bothered them during the previous 7 days and score each item from 0 to 4: not at all (0), a little bit (1), somewhat (2), quite a bit (3), and very much (4). The total score ranges from 0 to 32. A higher score reflects a more severe somatic symptom burden. SSS-8 will be conducted at baseline, 32 weeks gestation and 3 months postpartum.

Tachikawa Resilience Scale (TRS)

Resilience will be measured by TRS.[37] TRS consists of 10 items. All items are scored on a 7-point scale from 1 (strongly disagree) to 7 (strongly agree), with a total score ranging from 10 to 70. Higher scores reflect higher resilience. TRS will be conducted at baseline, 32 weeks gestation

and 3 months postpartum.

The Insomnia Severity Index (ISI)

Insomnia will be measured by the Japanese version of ISI.[38,39] ISI consists of 7 items assessing the severity of sleep-onset and sleep maintenance difficulties (both nocturnal and early morning awakenings), satisfaction with the current sleep pattern, interference with daily functioning, awareness of impairment attributed to the sleep problem, and degree of distress or concern caused by the sleep problem. Each item is rated on a 0 to 4 scale and the total score ranges from 0 to 28. A higher score suggests more severe insomnia. ISI will be conducted at baseline, 32 weeks gestation and 3 months postpartum.

Cambridge-Hopkins questionnaire short form (CH-RLSq13)

Restless legs syndrome (RLS) will be measured by the Japanese version of CH-RLSq13.[40,41] CH-RLSq13 consists of 13 items. Diagnosis of RLS is performed using 10 items consisting of questions about discomfort and stiffness of the lower limbs. In addition, 2 items ask about the degree of pain and the frequency of occurrence and 1 item asks about the age of onset (relevant to pregnancy in women). CH-RLSq13 will be conducted at baseline, 32 weeks gestation and 3 months postpartum.

Maternal Anxiety Scale for 4-5-month-old children

Maternal anxiety will be measured by the Maternal Anxiety Scale for 4-5-month-old children.[42] This scale consists of 34 items. Eleven items assess childcare anxiety, 6 items assess

husbands' or partners' support, 5 items assess childcare satisfaction, 4 items assess ease of raising children, 5 items assess a lack of confidence, and 3 items assess presence or absence of advisors. All items are scored on a 4-point scale from 1 (strongly disagree) to 4 (strongly agree). A higher score of each subscale reflects a higher presence of each factor. This scale will be conducted at 3 months postpartum.

Medical economic costs

For cost-effectiveness analysis, the presence or absence, frequency and duration of medical service use, and the use of drugs over the prior three months will be asked at 32 weeks gestation and 3 months postpartum.

Process evaluation

Implementation outcomes

Time spent logged in to each module will be measured. Also, we will evaluate implementation outcomes by self-report. Proctor and colleagues suggested 8 conceptually distinct implementation outcomes: acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, penetration, and sustainability.[43] However, a systematic review examined implementation outcomes for mental health and behavioral health using evidence-based rating criteria and concluded that the majority of instrumental outcomes were underdeveloped.[44] Recently, Weiner et al. developed measures of acceptability, appropriateness, and feasibility because their outcomes are often used as leading indicators and are conceptually distinct.[45] Three of the authors (DN, EO, NS) reviewed the

previous literature and selected the possible outcomes for each dimension of acceptability, appropriateness, and feasibility. These implementation outcomes and satisfaction with the intervention program will be asked about at 34 weeks gestation.

Adverse effects

Three of the authors (DN, EO, NS) reviewed the previous literature based on a systematic review, and selected the possible adverse effects of the program, such as physical symptoms (e.g., tired eyes, stiff shoulders), mental symptom (e.g., insomnia), dangerous experiences (e.g., collide with people while walking and looking at the smartphone), too much use of the smartphone, and excessive pressure to learn this program regularly. These potential adverse effects will be asked about at 34 weeks gestation.

Data collection

All data will be collected by the internet. If the entered data is incomplete, participants will not be able to proceed the assessment.

Sample size calculation

Required sample size was calculated for the primary outcome. New onset of MDE during the observation period in Japan and the effect size in hazard ratio are estimated to be 5% and 0.65,[46] based on previous studies. Thirty percent of participants are expected to drop out of the follow-up assessment. Given an α level of 0.05 (two-tailed) and a β level of 0.20, power Cox was performed with

STATA 14.0 and the appropriate sample size was calculated to be 4812. Since a large number of participants using the app will be recruited on one day, it is considered difficult to stop recruiting immediately when the sample size is reached. Thus, the sample size was set at 5,000.

Randomization

Participants who meet the inclusion criteria will be randomly allocated to the intervention group or control group. Participants will be stratified into two strata according to the score of K6 (4 or less, or 5 or more) on the baseline survey. MTI Ltd. will send baseline data stored in the cloud to researchers. In addition to the analysis of the whole sample (to examine the universal intervention effect), we will also analyze data by prespecified subgroups (to examine the selective intervention effect). Using a computer-generated random allocation sequence, an independent biostatistician created a stratified permuted-block random table. The block size of this RCT will be fixed at 4. The stratified permuted-block random table will be password protected and blinded to the researcher. Only the research assistant will be able to access it during the work of random allocation. MTI Ltd. will make the study participants allocated to the intervention group available to view the iCBT program on the app, based on the allocation provided by the research assistant.

Statistical methods

Main analysis

A survival analysis will be conducted to test for the effectiveness of the intervention on the time to the onset of MDE while controlling for censoring effects due to the differential length of follow-up or the completion of follow-up without an onset of MDE. Length of follow-up for each participant will be represented by either the number of months between the baseline and the onset of MDE or the end of the follow-up period (3-month postpartum, or 32 weeks gestation if a participant dropped out at the 3-month postpartum follow-up), whichever comes first. The cumulative incidence of MDE at the 32 weeks gestation and 3-month postpartum follow-up, as well as event-free survivals at every follow-up month, will be estimated using the Kaplan–Meier method; the statistical significance will be tested of the difference between the cumulative proportions of having MDE at 32 weeks gestation and 3-month postpartum follow-ups in the intervention and control groups. A log-rank test will be conducted to test the difference in survival probabilities between the intervention and the control groups. A single covariate Cox discrete time hazard model will also be used to test the difference and estimate the hazard ratio (HR), with 95% confidence intervals (CIs), for having MDE in the intervention group compared to the control group. The intervention effect will also be estimated, adjusting for dependent censoring and using the inverse probability of the censoring weighted (IPCW) method for conducting a sensitivity analysis.[47] The number needed to treat (NNT) to achieve prevention of one case of the onset of MDE will be calculated at 32 weeks gestation and 3-month postpartum follow-ups. A similar Cox discrete time hazard model also will be conducted using the two types of sub-threshold diagnoses of depressive episodes to investigate the effects of iCBT on

preventing depressive episodes, including subclinical cases. An intention-to-treat (ITT) analysis will be conducted.

Secondary analyses

For secondary outcomes (i.e. EPDS, K6, SSS-8, TRS), mixed models for repeated measures analyses will be conducted using a group (intervention or control) × time (baseline, 32 weeks gestation, 1 week postpartum or 3-month postpartum follow-up) interaction as an indicator of the intervention effect. The level of statistical significance for all analyses in this study will be set at 0.05 (two-tailed), and 95% CIs will be calculated. The effect size will be estimated in two ways. First, we will estimate a regression coefficient for a group (the intervention group vs. the control group) x time (baseline and follow-ups) interaction using the MIXED procedure, which will be converted to an effect size by dividing by a pooled SD at baseline and at follow-ups. Second, we will calculate Cohen's d among completers at baseline for each follow-up. ITT will be conducted as well. All statistical analyses will be conducted using SPSS Statistics 21.0 (IBM Corp., USA).

Subgroup analysis

The effectiveness of the programs may differ according to the initial severity of psychological distress. Therefore, we will use the stratification factor (i.e., participants who scored 4 or less/5 or more in K6 at the baseline survey) and analyze the results according to the prespecified subgroups.

Cost-effectiveness analysis

Quality-adjusted life-years (QALYs) will be calculated as the effectiveness, using the EQ-

5D-5L, as the area under the curve defined by the unitality values at baseline and follow-ups.[48] As for the costs, the cost of medical service use will be calculated based on the Survey of Medical Care Activities in Public Health Insurance,[49] which shows the treatment expenses covered by public health insurance in each diagnostic category. No intervention costs such as salary for therapists will be calculated because the program is fully-automated. Mean differences for the calculated effectiveness and costs will be compared between the intervention and control group.

Data monitoring and auditing

Because the iCBT program is not regarded as an invasive intervention, it is not necessary to set up a data monitoring board or to complete auditing in this trial.

Data availability

Deidentified individual participant data will be available upon reasonable request after publication of the main analysis paper. Contact information is the email address of the corresponding author.

Patient and public involvement

We utilized the function of the app “Luna Luna Baby” that allows users (pregnant women) to talk to each other about their problems. We extracted essential topics that pregnant women are concerned about based on 6393 text data, and developed programs for those topics. The topics were

extracted by using a machine learning approach, based on the Latent Dirichlet Allocation (LDA).[50] In this approach, morphological analysis was conducted for the text data from the pregnant women, and nouns and adjectives about what they suffer were collected. The LDA model was implemented by Scikit-learn version 0.21.3 (1) in Python. As a result, five topics were extracted: relationship with partners, concern about weight gain, concern about pregnancy checkup, physical symptoms such as pain, and dysfunction due to morning sickness. Since pregnancy checkup is considered to be a matter of obstetrics, each module of the iCBT program has been developed to deal with the remaining 4 topics, namely, module 1, 2 and 4 focus on dysfunction due to morning sickness, module 3 on concern about weight gain, module 5 on physical symptoms, and module 6 on relationship with partners. We will not access this chatroom during the RCT.

In addition, three women who had experiences of pregnancy and childbirth (two researchers and an ordinary mother) were invited to make comments on the intervention programs based on their experiences and preferences. Two researchers above (EO, NS) also were involved in designing this protocol.

Ethics and dissemination

Ethical and safety considerations

Informed consent for the app will be obtained from all participants included in this study after full explanation of the study. Candidates will be informed that their participation is voluntary,

and that even after voluntarily participating, they can withdraw from the study at any time and their withdrawal will cause no disadvantage to them. We expect no adverse health effects from this intervention, except possible deterioration in depressive symptoms. The principal investigators will communicate important protocol modification with the institutional review board.

Data confidentiality

The collected data will be stored as linkable anonymizing data. The principal investigator will have access to the final dataset after the trial and take responsibility for the integrity of the data and the accuracy of analysis.

Dissemination of research findings

The findings of this study will be disseminated through publications in peer-reviewed international journals. Presentations of the findings will also be offered at relevant research conferences, and local academic symposia and seminars. The principal investigator will be listed as corresponding authors, and the authorship eligibility will be conformed to the International Committee of Medical Journal Editors. If the intervention programs are found to be significantly positively effective, the programs can be made available for all users of the app in the future.

Discussion

The greatest strength of this study is to prove the effectiveness of the fully automated smartphone-based CBT program on preventing both antenatal and postpartum depression. The relatively short, newly developed programs for pregnant women would be practical and low dropout

is expected. Furthermore, this study will assess diagnosis of MDE using CIDI. Many previous studies using iCBT have suggested its preventive effect on depression; however, no previous studies assessed the diagnosis of perinatal depression using the structural interview. This RCT with large sample size can lead to a definitive result.

This study also will evaluate implementation outcomes of the program. Previous studies using iCBT have assessed the satisfaction with their program; however, few studies evaluated implementation outcomes including acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, penetration, and sustainability.[43] This study will contribute to the dissemination and implementation of iCBT in the future.

Another strength of this study is to add evidence of maternity blues. Maternity blues is highly prevalent, and it can present a range of symptoms such as intense short-lasting dysphoric mood, irritability, anxiety, sleep disturbance, and poor concentration within the first week following childbirth.[52] Maternity blues could lead to postpartum depression,[53] but to our knowledge, no previous studies have shown a preventive strategy to deal with maternity blues. This RCT will clarify whether iCBT during pregnancy can prevent maternity blues.

This study has several limitations. First, all outcomes will be measured by self-report, which could be affected by the perceptions of the participants. Second, users of the app are not regarded as representative of all pregnant women, though approximately 1 in 4 pregnant women in Japan are thought to use the app. Therefore, the findings of this study can not necessarily be generalizable.

Author contributions DN conceived and designed the study. DN, KI, EO, NS, and YS contributed creating programs. KW calculated sample size and developed analysis plan. DN wrote the first draft of the manuscript, and all other authors revised the manuscript critically. All authors approved the final version of the manuscript.

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Patient consent for publication Obtained.

Ethics approval The study plan was approved by the Research Ethics Review Board of Graduate School of Medicine/Faculty of Medicine, the University of Tokyo (2019150NI).

Figure legend:

Figure 1 Flow diagram of study participants

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Table 1 Contents of internet cognitive behavioral therapy program

Module No	Techniques for stress management
Module 1	Psychoeducation
Module 2	Case formulation based on cognitive behavioral model
Module 3	Behavioral activation
Module 4	Self-compassion
Module 5	Mindfulness
Module 6	Problem solving

Table 2 Overview of measurements

Measurement	Aim	Baseline (T1)	32 weeks gestation (T2)	34 weeks gestation (T3)	1 week postpartum (T4)	3 months postpartum (T5)
Primary outcomes						
CIDI	Diagnosis of Major Depressive Episode	✓	✓			✓
Secondary outcomes						
EPDS	Depressive symptoms	✓	✓		✓	✓
K6	Psychological distress	✓	✓		✓	✓
ED-5D-5L	Quality of life	✓	✓			✓
SSS-8	Somatic symptoms	✓	✓			✓
TRS	Resilience	✓	✓			✓
ISI	Insomnia	✓	✓			✓
CH-RLSq13	Restless legs syndrome	✓	✓			✓
Maternal Anxiety Scale for 4-5 months children	Maternal anxiety					✓
Medical costs	Medical service use	✓	✓			✓
Implementation and satisfaction	Implementation outcomes			✓		
Adverse effects	Physical and mental symptoms			✓		
Baseline assessments						
Demographics		✓				
VAWS		✓				

CIDI, World Health Organization Composite International Diagnostic Interview 3.0; EPDS, The Edinburgh Postnatal Depression Scale; K6, Kessler's Psychological Distress Scale; ED-5D-5L, EuroQol -5 dimension-5 level; SSS-8, Somatic symptom Scale-8; TRS, Tachikawa Resilience Scale; ISI, The Insomnia Severity Index; CH-RLSq13, Cambridge-Hopkins questionnaire short form; VAWS, Violence Against Women Screen

(Consent form in Japanese)

同　意　書

東京大学医学系研究科長・医学部長　殿

研究課題「全自動化インターネット認知行動療法による妊娠うつ病・産後うつ病の予防」
（審査番号＊＊＊＊）

私は、上記研究への参加にあたり、下記の説明文書の記載事項について説明を受け、これを十分理解しましたので本研究の研究対象者となることに同意いたします。

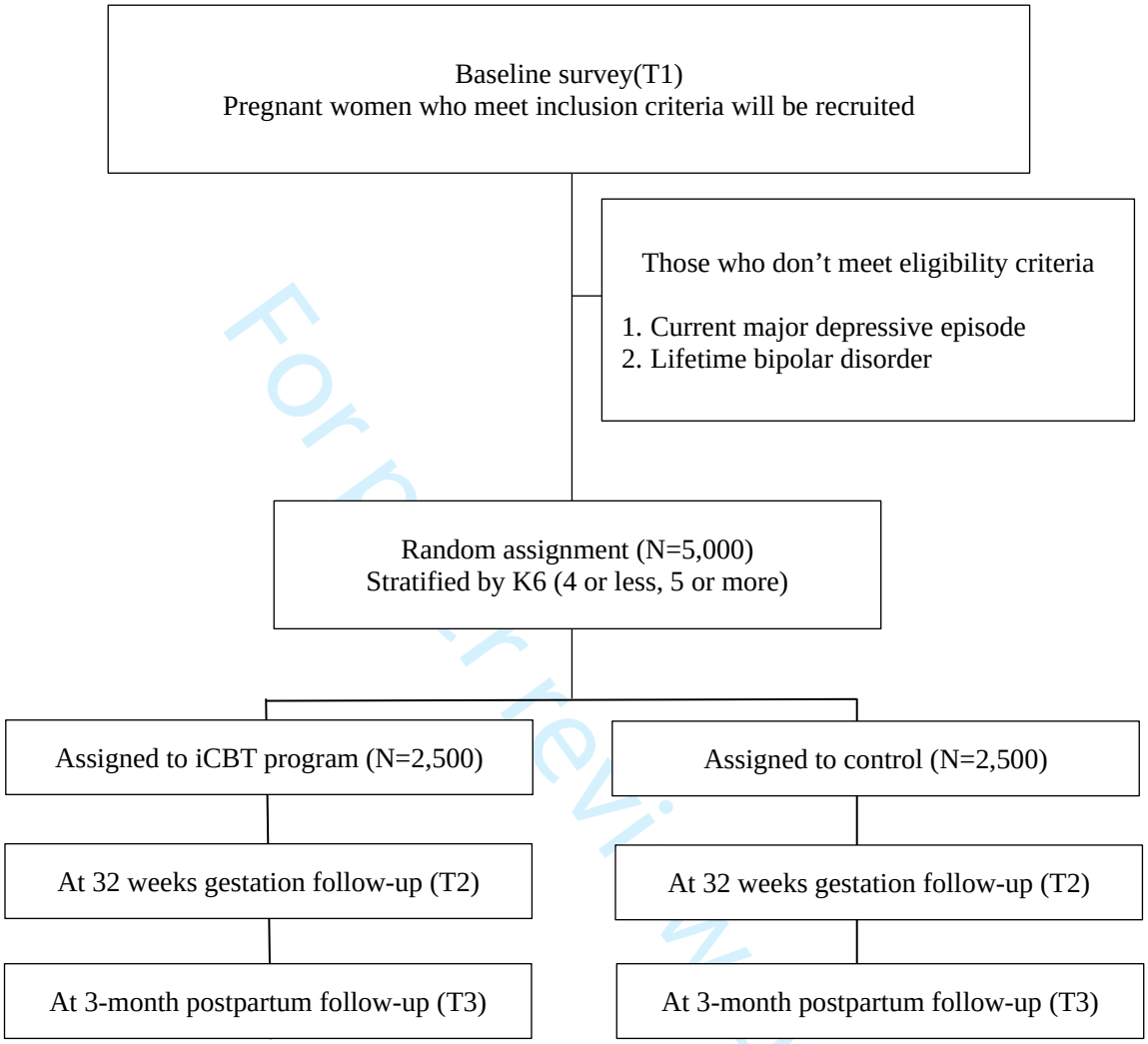
□　１、この研究の概要
□　２、研究参加の任意性と撤回の自由
□　３、個人情報の保護
□　４、研究結果の公表・開示
□　５、研究対象者にもたらされる利益及び不利益
□　６、研究終了後の資料（試料）等の取扱方針
□　７、あなたの費用負担
□　８、研究から生じる知的財産権の帰属
□　９、その他

また、私に関わるデータは、将来、新たに計画・実施される研究のために、長期間の保存と研究への使用に同意いたします。

□はい　　□いいえ

※同意の日付及び同意した人の ID はデータとして取得する。

Figure 1



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.

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

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		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	NA
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	23
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	23
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	NA
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	NA
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	NA

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-5
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	7-10
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)	NA
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
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	10-14

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)	6-7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7
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	16
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	16

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
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	NA
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 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	7

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	7
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	15
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	16-17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17-18
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)	16-18
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	18-19

		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
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	15
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
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)	20

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6, 20
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	20
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
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	20
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	NA
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	21

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	21
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	NA
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	NA

BMJ Open

Internet-based cognitive behavioral therapy for prevention of depression during pregnancy and in the postpartum (iPDP): a protocol for a large scale randomized controlled trial

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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Public health
Keywords:	MENTAL HEALTH, Depression & mood disorders < PSYCHIATRY, PREVENTIVE MEDICINE

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Title: Internet-based cognitive behavioral therapy for prevention of depression during pregnancy and in the postpartum (iPDP): a protocol for a large scale randomized controlled trial

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Abstract

Introduction: The objective of this randomized controlled trial (RCT) is to examine the effects of smartphone-based cognitive behavioral therapy (CBT) in preventing the onset of major depressive episodes (MDE) among pregnant women.

Methods and analysis: The target study population will be pregnant women of 16 to 20 weeks gestation who are currently users of "Luna Luna Baby," the most widely used app for pregnant women in Japan. Those who meet the eligibility criteria will be randomly allocated to the 6-module internet cognitive behavioral therapy (iCBT) program that was newly developed for pregnant women (n=2500), or to a treatment-as-usual control group (n=2500). Participants in the intervention groups will be required to complete the program by 32 weeks gestation. The primary outcomes are the number of new onsets of MDE, measured by using the World Health Organization Composite International Diagnostic Interview 3.0 (WHO-CIDI 3.0) at 32 weeks gestation and 3 months postpartum. Survival analysis will be conducted to test for the effectiveness of the intervention on the time to the onset of MDE.

Ethics and dissemination: The study plan has been approved by the Research Ethics Review Board of the Graduate School of Medicine/Faculty of Medicine, the University of Tokyo (2019150NI). If the intervention programs are found to produce a significant positive effect in this RCT, these programs can be made available for all users of the app in the future.

Keywords: smartphone-based cognitive behavioral therapy, antenatal depression, postpartum depression, prevention

Trial registration number: UMIN000038190; Pre-results.

Issue date: 16th, Dec, 2019

Article Summary

Strengths and limitations of this study

- The large sample size of this RCT can lead to a definitive result of the effectiveness of the fully automated smartphone-based CBT program in preventing both antenatal and postpartum depression.
- The newly developed program was tailored for pregnant women by extracting essential topics for them based on data from consultations on pregnant women's concerns.
- This study will also evaluate the implementation outcomes of iCBT program, which will contribute to the dissemination and implementation of iCBT.
- This RCT will also clarify whether iCBT during pregnancy can prevent maternity blues.
- A limitation of this study is that all of the outcomes will be measured by self-report.

Introduction

Prevention of perinatal depression is a critical public health issue.[1] The prevalence of antenatal depression was reported to be 7.4% in the first trimester, 12.8% in the second trimester, and 12.0% in the third trimester;[2] and the prevalence of postpartum depression was estimated to be 17.7%, though there is significant heterogeneity across nations.[3] Antenatal depression is associated with failing to seek prenatal care, an inadequate diet and/or use of tobacco, alcohol, or other harmful substances, self-harm or attempted suicide, and postpartum depression; while postpartum depression is associated with negative outcomes such as physical and psychological abuse to their children, and infanticide.[4] Furthermore, perinatal depression can also affect development from fetus to adolescent and paternal depression.[5-10] Therefore, preventing perinatal depression in the antenatal period is crucially important.

Given the large number of pregnant women who have risk factors such as maternal anxiety, life stress, lack of social support, unintended pregnancy, domestic violence, lower income and education, and poor relationships, making it difficult to identify and screen all high-risk pregnant women,[11] universal prevention should be more valued. According to a systematic review and meta-analysis, psychological interventions have been recommended as the most effective approach to prevent antenatal and postpartum depression.[12] Cognitive behavioral therapy (CBT) has been broadly researched and reported to be highly effective among psychological interventions.[13,14] Previous meta-analyses showed that the effect size of psychological intervention as universal prevention, which refers to approaches designed for the whole population regardless of individual risk factors, for postpartum depression was reported to be 0.19[15] and 0.37.[13] The timing of interventions of RCTs included in these meta-analyses were both during pregnancy and postpartum.

With respect to universal prevention, fully automated internet-based CBT (iCBT) is preferable to face-to-face or guided iCBT in terms of accessibility, anonymity, and cost-effectiveness.[16] Although a systematic review showed a positive effect of iCBT for the improvement of perinatal

depressive symptoms,[17] to our knowledge, there have been only two randomized controlled trials (RCTs) for universal prevention using automated iCBT during pregnancy.[18,19] These two studies did not assess the major depressive episode (MDE); instead, they used depressive symptoms as outcomes. In addition, a dropout from iCBT in these studies was relatively high (66% and 44%, respectively). A large number of sessions and/or the length per session may be impractical for a substantial number of pregnant women to complete, which may cause a high dropout rate. Thus, it would be necessary to develop a program that is more acceptable and feasible for pregnant women. In this regard, 6-sessions of 5 to 10-minutes iCBT programs were shown to be effective for preventing depressive symptoms for workers.[20]

Moreover, to our knowledge, no previous randomized controlled trials (RCTs) have examined the effect of iCBT on maternity blues. Maternity blues were characterized by psychological distress with a peak at 3 to 5 days after childbirth, though diagnostic criteria have not been well established. Maternity blues are highly prevalent and have been shown to be a risk factor for postpartum depression [21]; thus, it will be relevant to develop the intervention to prevent not only perinatal depression but also maternity blues.

The primary objective of this RCT is to examine the effectiveness of the newly developed 6-sessions of 5 to 10-minutes, smartphone-based, automated iCBT programs in preventing the onset of MDE at the third trimester and 3-months postpartum among pregnant women currently in the second trimester. The secondary objectives are to examine the effectiveness of iCBT for preventing maternity blues. The program would be practical and could be utilized by many pregnant women. In addition, intervention during early pregnancy will enable the prevention of not only postpartum depression but also antenatal depression.

Methods and Analysis

Trial design

The study will be a two-arm, parallel-group, treatment-as-usual (TAU) controlled, randomized trial. The allocation ratio of the intervention groups to the control group is 1:1. Random assignments are stratified by Kessler's Psychological Distress Scale (K6) scores (groups of 4 points or less and groups of 5 points or more) in the baseline survey. K6 is a self-report questionnaire, which assesses psychological distress during the past 30 days. Users of the app ("Luna Luna Baby" run by MTI Ltd.) will be recruited. The app provides the users for the growth of the fetus and the mental and physical condition of the pregnant women according to the number of gestation weeks. Users register the date of the last menstruation in the app; thus, we can find out the number of weeks of pregnancy.

Follow-up assessments will be conducted at 32 weeks gestation and 3-months postpartum. This protocol is written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guideline checklist.[22] The trial start date was the 27th of November, 2019, and the last follow-up date will be the 31st of March, 2021.

Participants

Pregnant women who have user IDs for the latest version of the app and meet the following criteria will be invited to participate in this RCT. Both primipara and multiparous women will be included.

Eligibility criteria

1. Being over 20 years old

2. Being 16 to 20 weeks gestation

3. Not diagnosed with a MDE in the past month by the web-based self-administered version of the WHO Composite International Diagnostic Interview 3.0 (WHO-CIDI 3.0)[23]

4. Not diagnosed with lifetime bipolar disorder (WHO-CIDI 3.0)

Recruitment

Figure 1 shows the study flow of this trial. MTI Ltd. sends an invitation message to potentially eligible pregnant women, which will include an explanation of the study and information on the eligibility criteria. After reading the explanation of the study, potential participants will be invited to give their consent on the app to participate in the study and to complete and return the baseline survey. MTI Ltd. will also send messages to study participants to join in follow-up assessments.

Five thousand pregnant women will be randomized to either the intervention group (n=2500), or the control group (n=2500). Participants in the intervention groups will be required to complete the intervention program up to 32 weeks gestation. Participants will be asked not to share this information through any social network. The participants will be reminded by a popup message to complete the program if they have not already done so. Intervention programs will be closed at 32 weeks gestation.

Participants in the control group will not receive any intervention programs during the intervention and follow-up period. General information about mental health during pregnancy will be provided to participants in both the intervention group and the control group as a TAU.

Interventions

A smartphone-based six-module CBT program designed for pregnant women was newly developed. Specifically, the first author (DN) developed the iCBT program with the collaboration of co-authors (KI, EO, NS, and YS). The program was tailored for pregnant women by extracting essential topics that pregnant women are concerned about. The details were shown in patient and public involvement section. This program will be provided via the Luna Luna Baby app, so users of the app don't have to download another app. Some components of the modules were derived from a previous iCBT program that successfully prevented the onset of MDE among office workers.[20] Other components such as behavioral activation based on values, self-compassion, and mindfulness have been incorporated, which could be regarded as the third wave CBT. The six modules are presented in a fixed order, with one module accessible per week, from module 1 to module 6 (Table 1). It will take

about 5 min to complete each module. The program includes psychoeducation (module 1), case formulation based on a cognitive behavioral model (module 2), behavioral activation (module 3), self-compassion (module 4), mindfulness (module 5), and problem-solving (module 6). Details of each of the components are as follows.

Psychoeducation (module 1)

In this module, participants learn about the roles of what are generally called "negative" emotions such as anxiety, depressive mood and anger. Each emotion is necessary for us; for example, anxiety is a sign that warns us of some risk in the future and promotes us to prepare for the future. This module was designed to help participants face and deal with their own emotions in subsequent modules. As an example of anxious situations, a scene that a partner of a pregnant woman is busy working and is not at home is used. As an example of sad situations, a scene when a pregnant woman suffers from morning sickness but the boss does not understand is used.

Case formulation based on cognitive-behavioral model (module 2)

In this module, participants learn about a cognitive-behavioral (CB) model, especially the five-part model (situation, thoughts, emotions, behavior, and physical sensations) and a case formulation based on this model.[24] Case formulation is a method used to understand the problems of patients or clients. Case formulation is helpful for participants to choose an appropriate approach to change the vicious circles of these five areas. A scene when a pregnant woman suffers from morning sickness but the boss does not understand is used as a case.

Behavioral activation (module 3)

Behavioral activation is a process to increase pleasurable and rewarding activities using behavioral strategies such as activity scheduling. This module provides a behavioral activation technique for enhancing participants' liveliness. In this module, participants learn about the theory of behavioral activation and how to plan an activity schedule to increase pleasant activities. Participants are also encouraged to identify their values based on brief behavioral activation therapy for depression

(BATD),[25] and acceptance and commitment therapy (ACT).[26] A scene when a pregnant woman would not like to go out because she has gained weight and is not motivated is used as a case.

Self-compassion (module 4)

Self-compassion indicates a positive and caring attitude of a person towards herself in the face of stressful events.[27] As a result of this attitude, highly self-compassionate individuals are expected to experience higher individual well-being.[28] Three interrelated determine the self-compassionate reactions to negative events and experiences: self-kindness, sense of common humanity and mindfulness. In this module, participants learn the concept of self-compassion and how to express compassion towards themselves. A scene when a pregnant woman suffers from morning sickness and is blaming herself for not being able to work as usual is used as a case.

Mindfulness (module 5)

Mindfulness is defined as "paying attention in a particular way: on purpose, in the present moment, and nonjudgmentally".[29] Mindful persons are likely to be aware of the physical sensation, thoughts, and emotions at that moment, which enables them to stop their usual reactions to a stressful event so that symptoms and problematic behaviors are likely to disappear. In this module, participants learn about the concept of mindfulness and how to practice it through listening to voice guidance. A scene when a pregnant woman feels anxiety due to tension and pain in the lower abdomen in spite of obstetrically normal is used as a case.

Problem-solving (module 6)

Problem-solving technique is a CB intervention that focuses on training adaptive problem-solving attitudes and skills.[30] A rational problem-solving style contains the systematic application of four problem-solving skills: (1) problem definition and formulation, (2) generation of alternative solutions, (3) decision making and (4) solution implementation and verification. In this module, participants learn about problem-solving skills to sort out the problem and make a list of solutions, and assertiveness to communicate with their partners confidently. A scene when a pregnant woman wants

her partner to do more in housework and childcare is used as a case.

Outcomes

Table 2 shows an overview of the outcome measures. Those who have not responded by more than a week after the online questionnaire is distributed will receive a popup message to complete each assessment.

Primary outcome

The primary outcome is the onset of MDE during the 32 weeks gestation and 3 months postpartum. The onset of MDE during the follow-up will be assessed using the web-based self-administered version of the Japanese WHO-CIDI 3.0 depression section, according to DSM-IV-TR criteria. The web version has been shown to have a good concordance with the clinical diagnosis of MDE and to be reliable in a 1-year test-retest survey. An incident case with MDE will be identified if a respondent reports an episode of MDE at either 32 weeks gestation or 3 months postpartum. An onset month for an episode of MDE also will be requested. In addition, two other definitions are applied to identify sub-threshold depressive episodes: one requires a shorter duration of symptoms (i.e. 7 days or more, rather than 2 weeks or more); the other one requires having a fewer symptoms (i.e. having 3 symptoms or more, instead of 5 symptoms or more).

Secondary outcomes

The Edinburgh Postnatal Depression Scale (EPDS)

Depressive symptoms will be measured by the Japanese version of EPDS [31, 32]. EPDS is used most often for screening perinatal depression because it focuses on cognitive symptoms of depression and excludes somatic items that can generate false positives during pregnancy and postpartum. It consists of 10 items, with 0-3 points scored per item for a potential scale score of 0-30. The higher scores indicate more severe depressive symptoms. EPDS will be conducted at baseline, 32 weeks gestation, 1 week postpartum and 3 months postpartum.

Kessler's Psychological Distress Scale (K6)

Psychological distress is measured by the Japanese version of K6.[33,34] K6 consists of six items assessing the frequency with which respondents have experienced symptoms of psychological distress during the past 30 days. The response options range from 0 (none of the time) to 4 (all of the time), and the total score ranges from 0 to 24. The higher scores indicate more severe psychological distress. K6 will be conducted at baseline, 32 weeks gestation, 1 week postpartum and 3 months postpartum.

EuroQol -5 dimension-5 level (ED-5D-5L)

General health status will be measured by the Japanese version of EQ-5D-5L.[35-37] It is a 5-dimensional utility instrument consisting of domains about morbidity, self-care, usual activities, pain or discomfort, and anxiety or depression. Each domain is divided into 5 levels of severity (none, slight, moderate, severe, extreme problems, or unable to). All responses are converted into a single index score of general health status. ED-5D-5L will be conducted at baseline, 32 weeks gestation and 3 months postpartum.

Somatic symptom Scale-8 (SSS-8)

Somatic symptoms will be measured by Japanese version of SSS-8.[38,39] SSS-8 consists of 8 items that assess the following symptoms: stomach or bowel problems; back pain; pain in the arms, legs, or joints; headaches; chest pain or shortness of breath; dizziness; feeling tired or having low energy; and trouble sleeping. These items comprise the four symptom domains of gastrointestinal, pain, cardiopulmonary, and fatigue. Respondents rate how much each symptom has bothered them during the previous 7 days and score each item from 0 to 4: not at all (0), a little bit (1), somewhat (2), quite a bit (3), and very much (4). The total score ranges from 0 to 32. A higher score reflects a more severe somatic symptom burden. SSS-8 will be conducted at baseline, 32 weeks gestation and 3 months postpartum.

Tachikawa Resilience Scale (TRS)

Resilience will be measured by TRS.[40] TRS consists of 10 items. All items are scored on a 7-point scale from 1 (strongly disagree) to 7 (strongly agree), with a total score ranging from 10 to 70. Higher scores reflect higher resilience. TRS will be conducted at baseline, 32 weeks gestation and 3 months postpartum.

The Insomnia Severity Index (ISI)

Insomnia will be measured by the Japanese version of ISI.[41,42] ISI consists of 7 items assessing the severity of sleep-onset and sleep maintenance difficulties (both nocturnal and early morning awakenings), satisfaction with the current sleep pattern, interference with daily functioning, awareness of impairment attributed to the sleep problem, and degree of distress or concern caused by the sleep problem. Each item is rated on a 0 to 4 scale and the total score ranges from 0 to 28. A higher score suggests more severe insomnia. ISI will be conducted at baseline, 32 weeks gestation and 3 months postpartum.

Cambridge-Hopkins questionnaire short form (CH-RLSq13)

Restless legs syndrome (RLS) will be measured by the Japanese version of CH-RLSq13.[43,44] CH-RLSq13 consists of 13 items. Diagnosis of RLS is performed using 10 items consisting of questions about discomfort and stiffness of the lower limbs. In addition, 2 items ask about the degree of pain and the frequency of occurrence and 1 item asks about the age of onset (relevant to pregnancy in women). CH-RLSq13 will be conducted at baseline, 32 weeks gestation and 3 months postpartum.

Maternal Anxiety Scale for 4-5-month-old children

Maternal anxiety will be measured by the Maternal Anxiety Scale for 4-5-month-old children.[45] This scale consists of 34 items. Eleven items assess childcare anxiety, 6 items assess husbands' or partners' support, 5 items assess childcare satisfaction, 4 items assess ease of raising children, 5 items assess a lack of confidence, and 3 items assess presence or absence of advisors. All items are scored on a 4-point scale from 1 (strongly disagree) to 4 (strongly agree). A higher score of

each subscale reflects a higher presence of each factor. This scale will be conducted at 3 months postpartum.

Medical economic costs

For cost-effectiveness analysis, the presence or absence, frequency and duration of medical service use, and the use of drugs over the prior three months will be asked at 32 weeks gestation and 3 months postpartum.

Process evaluation

Implementation outcomes

Time spent logged in to each module will be measured. Also, we will evaluate implementation outcomes by self-report via survey. Proctor and colleagues suggested 8 conceptually distinct implementation outcomes: acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, penetration, and sustainability.[46] However, a systematic review examined implementation outcomes for mental health and behavioral health using evidence-based rating criteria and concluded that the majority of instrumental outcomes were underdeveloped.[47] Recently, Weiner et al. developed measures of acceptability, appropriateness, and feasibility because their outcomes are often used as leading indicators and are conceptually distinct.[48] Three of the authors (DN, EO, NS) reviewed the previous literature and selected the possible outcomes for each dimension of acceptability, appropriateness, and feasibility. These implementation outcomes and satisfaction with the intervention program will be asked about at 34 weeks gestation.

Adverse effects

Three of the authors (DN, EO, NS) reviewed the previous literature based on a systematic review, and selected the possible adverse effects of the program, such as physical symptoms (e.g., tired eyes, stiff shoulders), mental symptom (e.g., insomnia), dangerous experiences (e.g., collide with people while walking and looking at the smartphone), too much use of the smartphone, and excessive pressure to learn this program regularly. These potential adverse effects will be asked about at 34

weeks gestation.

Data collection

All data will be collected by the internet. If the entered data is incomplete, participants will not be able to proceed the assessment.

Sample size calculation

Required sample size was calculated for the primary outcome. New onset of MDE during the observation period in Japan and the effect size in hazard ratio are estimated to be 5% and 0.65,[49] based on previous studies. Thirty percent of participants are expected to drop out of the follow-up assessment. Given an α level of 0.05 (two-tailed) and a β level of 0.20, power Cox was performed with STATA 14.0 and the appropriate sample size was calculated to be 4812. Since a large number of participants using the app will be recruited on one day, it is considered difficult to stop recruiting immediately when the sample size is reached. Thus, the sample size was set at 5,000.

Randomization

Participants who meet the inclusion criteria will be randomly allocated to the intervention group or control group. Participants will be stratified into two strata according to the score of K6 (4 or less, or 5 or more) on the baseline survey. MTI Ltd. will send baseline data to researchers. In addition to the analysis of the whole sample (to examine the universal intervention effect), we will also analyze data by prespecified subgroups (to examine the selective intervention effect). Using a computer-generated random allocation sequence, an independent biostatistician created a stratified permuted-block random table. The block size of this RCT will be fixed at 4. The stratified permuted-block random table will be password protected and blinded to the researcher. Only the research assistant will be able to access it during the work of random allocation. MTI Ltd. will make the study participants allocated to the intervention group available to view the iCBT program on the app, based on the

allocation provided by the research assistant.

Statistical methods

Main analysis

A survival analysis will be conducted to test for the effectiveness of the intervention on the time to the onset of MDE while controlling for censoring effects due to the differential length of follow-up or the completion of follow-up without an onset of MDE. Length of follow-up for each participant will be represented by either the number of months between the baseline and the onset of MDE or the end of the follow-up period (3-month postpartum, or 32 weeks gestation if a participant dropped out at the 3-month postpartum follow-up), whichever comes first. The cumulative incidence of MDE at the 32 weeks gestation and 3-month postpartum follow-up, as well as event-free survivals at every follow-up month, will be estimated using the Kaplan–Meier method; the statistical significance will be tested of the difference between the cumulative proportions of having MDE at 32 weeks gestation and 3-month postpartum follow-ups in the intervention and control groups. A log-rank test will be conducted to test the difference in survival probabilities between the intervention and the control groups. A single covariate Cox discrete time hazard model will also be used to test the difference and estimate the hazard ratio (HR), with 95% confidence intervals (CIs), for having MDE in the intervention group compared to the control group. The intervention effect will also be estimated, adjusting for dependent censoring and using the inverse probability of the censoring weighted (IPCW) method for conducting a sensitivity analysis.[50] The number needed to treat (NNT) to achieve prevention of one case of the onset of MDE will be calculated at 32 weeks gestation and 3-month postpartum follow-ups. A similar Cox discrete time hazard model also will be conducted using the two types of sub-threshold diagnoses of depressive episodes to investigate the effects of iCBT on preventing depressive episodes, including subclinical cases. An intention-to-treat (ITT) analysis will be conducted. Multiple imputation will be performed.

Secondary analyses

For secondary outcomes (i.e. EPDS, K6, SSS-8, TRS), mixed models for repeated measures analyses will be conducted using a group (intervention or control) × time (baseline, 32 weeks gestation, 1 week postpartum or 3-month postpartum follow-up) interaction as an indicator of the intervention effect. This allow for missing data to be taken into account within the statistical model. The level of statistical significance for all analyses in this study will be set at 0.05 (two-tailed), and 95% CIs will be calculated. The effect size will be estimated in two ways. First, we will estimate a regression coefficient for a group (the intervention group vs. the control group) x time (baseline and follow-ups) interaction using the MIXED procedure, which will be converted to an effect size by dividing by a pooled SD at baseline and at follow-ups. Second, we will calculate Cohen's d among completers at baseline for each follow-up. ITT will be conducted as well. All statistical analyses will be conducted using SPSS Statistics 21.0 (IBM Corp., USA).

Subgroup analysis

The effectiveness of the programs may differ according to the initial severity of psychological distress. Therefore, we will analyze the results according to the prespecified subgroups (i.e., participants who scored 4 or less/5 or more in K6 at the baseline survey).

Cost-effectiveness analysis

Quality-adjusted life-years (QALYs) will be calculated as the effectiveness, using the EQ-5D-5L, as the area under the curve defined by the unitality values at baseline and follow-ups.[51] As for the costs, the cost of medical service use will be calculated based on the Survey of Medical Care Activities in Public Health Insurance,[52] which shows the treatment expenses covered by public health insurance in each diagnostic category. No intervention costs such as salary for therapists will be calculated because the program is fully-automated. Mean differences for the calculated effectiveness and costs will be compared between the intervention and control group.

Data monitoring and auditing

Because the iCBT program is not regarded as an invasive intervention, it is not necessary to set up a data monitoring board or to complete auditing in this trial.

Data availability

Deidentified individual participant data will be available upon reasonable request after publication of the main analysis paper. Contact information is the email address of the corresponding author.

Patient and public involvement

We utilized the function of the app "Luna Luna Baby" that allows users (pregnant women) to talk to each other about their problems. We extracted essential topics that pregnant women are concerned about based on 6393 text data, and developed programs for those topics. Even MTI, Ltd. cannot identify the person who posted a text, thus the text data is anonymized data that cannot be linked. The procedure was approved by the ethic committee of the University of Tokyo. The topics were extracted by using a machine learning approach, based on the Latent Dirichlet Allocation (LDA).[53] In this approach, morphological analysis was conducted for the text data from the pregnant women, and nouns and adjectives about what they suffer were collected. The LDA model was implemented by Scikit-learn version 0.21.3 [54] in Python. As a result, five topics were extracted: relationship with partners, concern about weight gain, concern about pregnancy checkup, physical symptoms such as pain, and dysfunction due to morning sickness. Since pregnancy checkup is considered to be a matter of obstetrics, each module of the iCBT program has been developed to deal with the remaining 4 topics. We will not access this chatroom during the RCT.

In addition, three women who had experiences of pregnancy and childbirth (two researchers and a research partner with lived experience) were invited to make comments on the intervention programs based on their experiences and preferences. All of them experienced maternity blues or

perinatal depression, though they did not visit psychiatrists. Two researchers above (EO, NS) also were involved in designing this protocol.

Ethics and dissemination

Ethical and safety considerations

Informed consent for the app will be obtained from all participants included in this study after full explanation of the study. Candidates will be informed that their participation is voluntary, and that even after voluntarily participating, they can withdraw from the study at any time and their withdrawal will cause no disadvantage to them. We expect no adverse health effects from this intervention, except possible deterioration in depressive symptoms. We will send messages to those who meet the criteria for MDE in the past month or for lifetime bipolar disorders at baseline to encourage them to see a psychiatrist. The principal investigators will communicate important protocol modification with the institutional review board.

Data confidentiality

The collected data will be stored as linkable anonymizing data. The principal investigator will have access to the final dataset after the trial and take responsibility for the integrity of the data and the accuracy of analysis.

Dissemination of research findings

The findings of this study will be disseminated through publications in peer-reviewed international journals. Presentations of the findings will also be offered at relevant research conferences, and local academic symposia and seminars. If important findings are obtained from this study, we will make a press release and provide a plain language summary for users of Luna Luna baby. The principal investigator will be listed as corresponding authors, and the authorship eligibility will be conformed to the International Committee of Medical Journal Editors. If the intervention programs are found to be significantly positively effective, the programs can be made available for

all users of the app in the future.

Discussion

The greatest strength of this study is to prove the effectiveness of the fully automated smartphone-based CBT program on preventing both antenatal and postpartum depression. The relatively short, newly developed programs for pregnant women would be practical and low dropout is expected. Furthermore, this study will assess diagnosis of MDE using CIDI. Many previous studies using iCBT have suggested its preventive effect on depression; however, no previous studies assessed the diagnosis of perinatal depression using the structural interview. This RCT with large sample size can lead to a definitive result.

This study also will evaluate implementation outcomes of the program. Previous studies using iCBT have assessed the satisfaction with their program; however, few studies evaluated implementation outcomes including acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, penetration, and sustainability.[46] This study will contribute to the dissemination and implementation of iCBT in the future.

Another strength of this study is to add evidence of maternity blues. Maternity blues is highly prevalent, and it can present a range of symptoms such as intense short-lasting dysphoric mood, irritability, anxiety, sleep disturbance, and poor concentration within the first week following childbirth.[55] Maternity blues could lead to postpartum depression,[56] but to our knowledge, no previous studies have shown a preventive strategy to deal with maternity blues. This RCT will clarify whether iCBT during pregnancy can prevent maternity blues.

This study has several limitations. First, all outcomes will be measured by self-report, which could be affected by the perceptions of the participants. Second, users of the app are not regarded as representative of all pregnant women, though approximately 1 in 4 pregnant women in Japan are thought to use the app. Therefore, the findings of this study can not necessarily be generalizable. Third,

follow-up period is not long enough, because a sizeable proportion of postpartum depression have onset after 3 months postpartum.

Author contributions DN conceived and designed the study. DN, KI, EO, NS, and YS contributed creating programs. NY and NK contributed to the development of study design. KW calculated sample size. KW and YM developed analysis plan. DN wrote the first draft of the manuscript, and all other authors revised the manuscript critically. All authors approved the final version of the manuscript.

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Patient consent for publication Obtained.

Ethics approval The study plan was approved by the Research Ethics Review Board of Graduate School of Medicine/Faculty of Medicine, the University of Tokyo (2019150NI).

Figure legend:

Figure 1 Flow diagram of study participants

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Table 1 Contents of internet cognitive behavioral therapy program

Module No	Techniques for stress management
Module 1	Psychoeducation
Module 2	Case formulation based on cognitive behavioral model
Module 3	Behavioral activation
Module 4	Self-compassion
Module 5	Mindfulness
Module 6	Problem solving

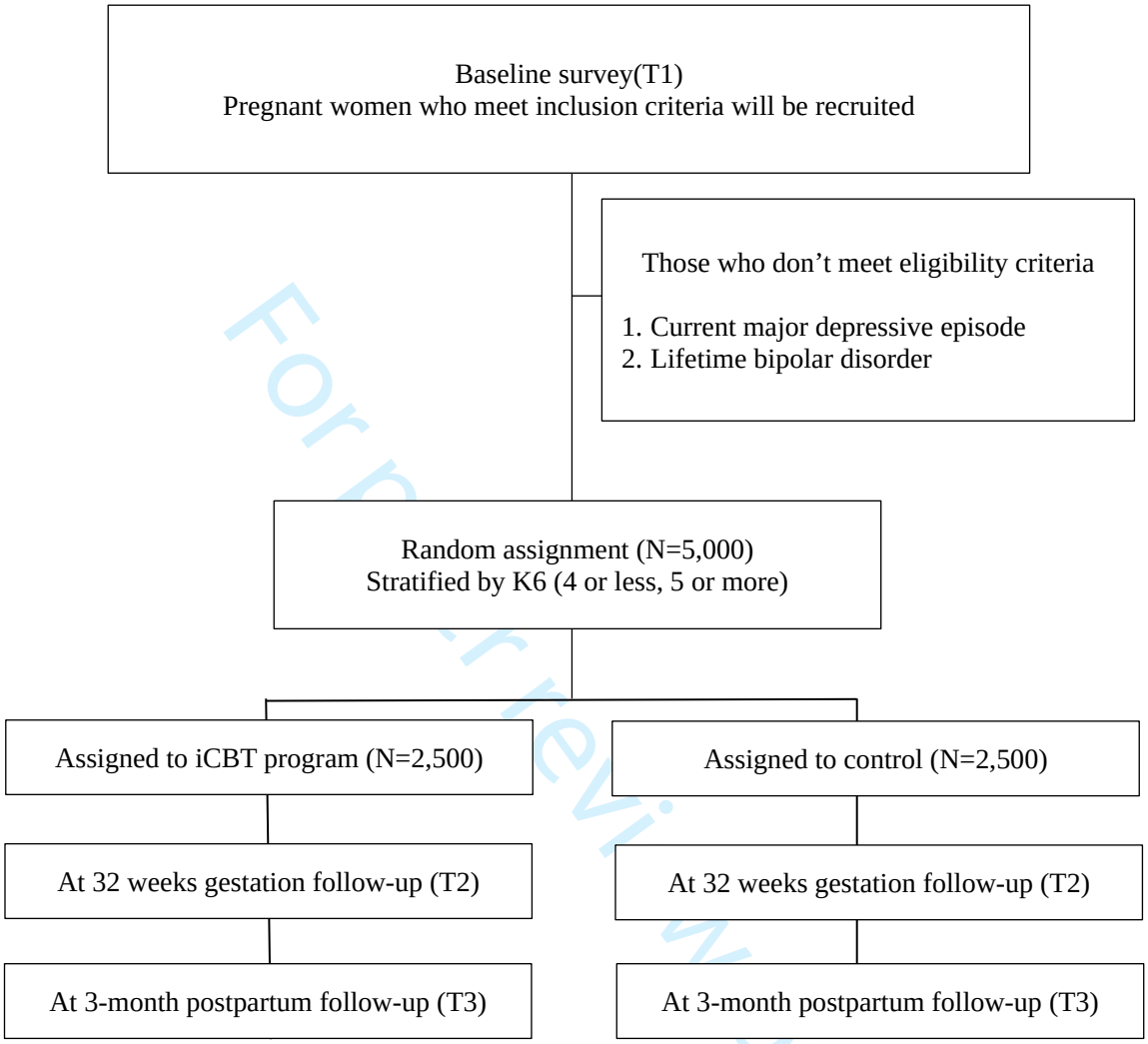
Table 2 Overview of measurements

Measurement	Aim	Baseline (T1)	32 weeks gestation (T2)	34 weeks gestation (T3)	1 week postpartum (T4)	3 months postpartum (T5)
Primary outcomes						
CIDI	Diagnosis of Major Depressive Episode	✓	✓			✓
Secondary outcomes						
EPDS	Depressive symptoms	✓	✓		✓	✓
K6	Psychological distress	✓	✓		✓	✓
ED-5D-5L	Quality of life	✓	✓			✓
SSS-8	Somatic symptoms	✓	✓			✓
TRS	Resilience	✓	✓			✓
ISI	Insomnia	✓	✓			✓
CH-RLSq13	Restless legs syndrome	✓	✓			✓
Maternal Anxiety Scale for 4-5 months children	Maternal anxiety					✓
Medical costs	Medical service	✓	✓			✓

	use		
Implementation and satisfaction	Implementation outcomes		✓
Adverse effects	Physical and mental symptoms		✓
Baseline assessments			
Demographics		✓	
VAWS		✓	

CIDI, World Health Organization Composite International Diagnostic Interview 3.0; EPDS, The Edinburgh Postnatal Depression Scale; K6, Kessler's Psychological Distress Scale; ED-5D-5L, EuroQol -5 dimension-5 level; SSS-8, Somatic symptom Scale-8; TRS, Tachikawa Resilience Scale; ISI, The Insomnia Severity Index; CH-RLSq13, Cambridge-Hopkins questionnaire short form; VAWS, Violence Against Women Screen

Figure 1



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:

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		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	NA
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	23
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	23
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	NA
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	NA
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	NA

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-5
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	7-10
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)	NA
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
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	10-14

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)	6-7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7
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	16
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	16

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
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	NA
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 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	7

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	7
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	15
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	16-17
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17-18
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)	16-18
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	18-19

		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
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	15
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
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)	20

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6, 20
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	20
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
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	20
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	NA
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	21

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	21
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	NA
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	NA