Study protocol and statistical analysis plan

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Brief Title: A Smartphone-Assisted Brief Behavioral Intervention for Pregnant Women With Depression

Principal investigator: Guilherme Vanoni Polanczyk

Date of document: 31/07/2020

HOSPITAL DAS CLÍNICAS OF THE FACULTY OF MEDICINE OF THE UNIVERSITY OF SAN PAULO-HCFMUSP

CONSENT FORM

RESEARCH DATA

Research Title: **Developing and Testing the Motherly App: An Intervention automated to promote the mental health of young mothers**

Main Researcher **: Guilherme Vanoni Polanczyk**

Department/Institute **: Department of Psychiatry FMUSP**

We invite you to participate in scientific research that seeks to create or increase knowledge about an important subject. The discoveries although they often do not bring direct benefits to the research participant, they may in the future be useful for many people. To decide whether or not to participate in this research, you need to understand enough about the risks and benefits, so you can make a conscious judgment. Initially we will explain the research reasons. Below, we will provide an informed consent form (TCLE), a document that contains information about the research, for you to read and discuss with family members and/or other people you trust. Once the research objective is understood and there is its interest in participating, your initials will be requested on all pages of the TCLE and your signature on the last page. A signed copy of this term must be retained by you or your representative legal status and a copy will be archived by the responsible researcher.

Rationale and objectives of the study : You are being invited to participate in a study about the development of a *smartphone* mobile application that aims to promote health and well-being of pregnant women and their children. This app, called Motherly, can help pregnant women to have a healthy pregnancy. The app can also help in reducing symptoms of depression. during pregnancy. Scientific works already suggest that technologies such as *smartphone* apps can improve physical and mental health. This study will test two types of apps, one with active elements related to sleep, nutrition, physical activity, prenatal care, support social, breastfeeding and stimulation of child development, and other educational information, articles and texts on the gestational period and child development. Both possibilities also include psychotherapy treatment to treat symptoms of depression and anxiety.

If you agree to participate in this study together with your child, you will be invited to perform a remote assessment of your feelings, behaviors, emotions and habits of approximately 1 hour and a half. During the study you will also answer short questions about these same themes through the app. When your child is 2 or 3 months old, we will invite you to answer questions about feelings, behaviors, emotions, habits and child development. If during the study emotional or behavioral problems are identified, you will be guided by a member of our team so that you can seek assistance. The other procedures pose minimal risk, as detailed below.

Procedures that will be carried out and methods that will be employed: You will be invited to be part of one of the follow-up groups for this study: the group that will receive the application Motherly or the group that will receive an educational app. Both groups will also receive psychotherapeutic assistance. Selection for participation in either of the two groups will be by lottery, as follows:

a) Motherly app group : you will be accompanied during the prenatal period and up to three months of your child's age. The Motherly app will provide information about the importance of healthy behaviors and maternal/infant health care for your child's future. Schedules, checklists and notifications will be available to help with follow-up prenatal doctor. The app will also help you schedule daily activities that help with reduction of depressive symptoms and increase the feeling of well-being. The app will give points and badges based on behaviors and interactions with other mothers. visual resources will present information to guide pregnant women, such as progress bars, rating of badges and dots. The Motherly app will actively help pregnant women to improve their mental health, sleep quality, nutrition, physical activity, social support, prenatal care and breast-feeding. You will also receive psychotherapeutic care in 4 sessions performed by a professional specialist in the field. **b) Motherly Educational App Group:** You will receive a *smartphone* mobile app with informative content in the form of short articles written by specialized professionals (pediatricians, psychologists, psychiatrists, nutritionists, physical educators). More specifically, the content will be related to health and pregnancy, with articles related to depression detection, nutrition, fetal and infant development, breastfeeding, sleep, physical activity. you will also receive psychotherapeutic care in 4 sessions performed by a specialist in the field.

How the routine procedures will be performed : The procedures described below will be carried out in all research participants, that is, the group that will receive the Motherly and group that will receive the educational Motherly app.

Child Development Assessment: We will ask about your child's development via application. The questions will be short and simple, such as "is your child able to sit up?" or “your child smiles?”. At the end of the study, when your child is 2-3 months old, we will apply a child development questionnaire with approximately 36 short questions.

Assessment of symptoms of depression, anxiety, well-being and sleep: we will ask weekly about your general well-being in a short and fast way via the app. Questions may be answered at the time you prefer and will generally be done two by two. **Physical activity assessment:** during the study the app will record data from a device present in every cell *phone* called an accelerometer, which measures acceleration. The data of the accelerometer are converted into steps, which then allow us to assess physical activity. These procedures will be carried out via the internet and cell *phone*. The *smartphone* app will have visuals that allow you to check the results of some of the questions performed. Also, if depression, anxiety or any other serious problem is detected, you will be notified and, if necessary, contacted by a member of our team. At the end of the study, you will be able to request a return of the completed questionnaires. We make it clear that the requested questionnaires are for research purposes and have no defined clinical meaning, being possible to define the diagnosis of a disease or mental health problem.

Risks and discomforts: There are no risks or discomforts involved, all procedures performed in this research will be non-invasive. The issues described above may cause some discomfort, but we emphasize that you do not need to answer questions that generate discomfort and you can continue participating in the survey and using the application.

You will benefit from psychotherapy services, which can help you cope with symptoms of depression and anxiety. Regarding the research results, it is important to say that scientific studies are based on the analysis of a large number of samples, making it impossible to estimate the individual benefit of each patient included in the study. It may be that the results of this study bring a benefit for a portion of patients in the future. These results can take many years to be achieved, so any benefit from this study, if any, will only be in the long term. This study has potential relevance to public health and is scientifically innovative in terms of testing an intervention using technology. The intervention proposal will be tested for the first time in the world with a strategy for the prevention and promotion of well-being in pregnant women with high potential for application in other places in Brazil and around the world. You will benefit from informative content relevant to the pregnancy, which can complement the medical follow-up. Participation in assessments can also help in detecting important aspects such as depression, anxiety, sleep quality, among others.

Secrecy and privacy: Your privacy and confidentiality will be respected, data will be treated anonymously by the researchers, who undertake and are responsible for the custody and confidentiality of data. The data obtained will only be used for the purpose foreseen in this project of research and any other use will require your consent.
Form of monitoring and assistance: At any stage of the study, you will have access to the professionals responsible for the research to clarify any doubts. If necessary or you ask us, we will send you a list of places that offer mental health care. There will be no specific follow-up to the survey after it ends, but if you do present any problem or personal damage arising from participation in the research, the right to immediate and free treatment by the researchers involved. You are free to refuse to participate or withdraw your consent at any stage of the research without any penalty, secrecy and privacy. If you are undergoing treatment at Child and Adolescent Psychiatry Service of the Psychiatry Institute of the Hospital das Clínicas, your follow-up will not change if you accept or decline to participate in this study.

Remuneration - There will be no personal expenses arising from the research, nor financial compensation related to your participation. Not excluding the possibility of indemnity determined by the resolution 466/2012, if the damage is due to the research. At any stage of the study, you will have access to the professionals responsible for the research. If you have any questions, you may contact the principal investigator, **Dr** . **Guilherme Vanoni Polanczyk** , which can be found at the **Institute of Psychiatry of the USP Faculty of Medicine**, **Rua Dr. Ovídio Pires de Campos, 785 – Cerqueira César – São Paulo – SP - 1st floor, room 08** , **wing south,** Telephone (11) 2661-7594, opening hours from 8 am to 12 pm, or **Dr. Daniel Graça Factori de Sá** , who can be found at the **Instituto de Psiquiatria do Hospital das Clínicas da FMUSP, Rua Dr. Ovídio Pires de Campos, 785 – Cerqueira César – São Paulo – SP - CEAPESQ, 3rd floor, room 9** , Telephone (11) 2661 7895, opening hours from **1pm** to 6pm. If you have any concerns or questions about research ethics, please contact the Ethics Committee for Analysis of Research Projects - **CAPPesq** – Rua Ovídio Pires de Campos, 225 – 5th floor – tel.: (11) 2661-7585, (11) 2661-1548, (11) 2661-1549, from 7 am to 4 pm, Monday to Friday or by email: cappesq.adm@hc.fm.usp.br .

I declare that I have been sufficiently informed about the study **Developing and testing the Motherly app: an automated intervention to promote the mental health of young people mothers.**

The objectives, procedures, potential discomforts and risks and the guarantees. I voluntarily agree to participate in this study, accept this Consent Form and I get a copy of it.

_____
Signature of participant/legal representative
Date____/____/_____

_____
Participant/Legal Representative Name

_____
Date____/____/_____
Signature of the person responsible for the study

Study protocol and statistical analysis plan

Smartphone-Assisted Brief Behavioral Intervention for Pregnant Women With Depression

Researchers: Pedro Fonseca Zuccolo, Alicia Matijasevich, Guilherme Polanczyk, Daniel Fatori

Affiliation: University of Sao Paulo Medical School

Trial Registration: NCT04495166

Background

Pregnancy is strongly associated with increased risk for depression. Approximately 25% of pregnant women develop depression. Treatment for depression during pregnancy has several complexities: the use of psychiatric medications during pregnancy might result in developmental problems in the child and must be used with caution. Psychosocial interventions are effective, but they require specialized professionals. Low- and middle-income countries (LMIC) countries such as Brazil do not have enough mental health professionals needed to meet this demand. In this context, smartphone-based interventions show immense potential. We developed Motherly, a smartphone application (app) designed to treat maternal depression. We aim to test the efficacy of Motherly in addition to brief cognitive-behavioral therapies (CBT) to treat maternal depression.

Objectives and outcomes

The efficacy of the Motherly app in conjunction with brief CBT (intervention) will be evaluated in a RCT in comparison with an app designed to offer educational content about gestation, maternal health and mental health, and child development in addition to brief CBT (active control).

The main objective of the study is to test the efficacy of a mental health intervention delivered via smartphone application in addition to brief CBT to reduce depressive symptoms and to promote maternal and child health and well-being in pregnant women with depression. Our primary outcome is the change in maternal prenatal depression from baseline to posttreatment (8 weeks). We will also test the efficacy of the intervention on secondary outcomes assessed during gestation: change in maternal mental health (prenatal anxiety, psychological well-being, perceived stress, depression, depression severity, and sleep quality) from baseline to posttreatment, change in maternal prenatal quality of life from baseline to posttreatment, and change in maternal physical activity levels from baseline to posttreatment. Additionally, we will conduct a postnatal follow-up when the child is 2 months of age to test the impact of the intervention on the following secondary outcomes: change in maternal mental health (postnatal depression symptoms, depression severity, anxiety, psychological well-being, perceived stress, and sleep quality) from baseline to follow-up, change in maternal postnatal quality of life from baseline to follow-up, infant developmental milestones, and social/emotional problems at 2 months of age.

Study protocol and statistical analysis plan

Hypotheses

Participants receiving the Motherly app in addition to brief CBT will show significantly greater reduction in symptoms of depression, as well as greater well-being, better overall mental health, and levels of physical activity compared with participants who receive only educational content in addition to brief CBT. We also predict that children of mothers from the intervention group will show better development in the first two months of age in comparison with children from participants in the active control group.

Methods

Setting and design

We plan to conduct a 2-arm parallel-randomized controlled clinical trial (RCT). We aim to include 70 pregnant women between 16-40 years old. Since all interventions will be conducted online, participants will be recruited from any Brazilian state or municipality. Participants will be randomly assigned to either receive intervention via app consisting of behavioral activation (BA) and psychoeducation to promote changes in sleep, nutrition, and physical activity habits, as well as to engage in prenatal care, breastfeeding, and social support, and to stimulate child development, in addition to brief cognitive-behavioral therapy (CBT) (n=35); or to a active control group receiving an educational app with content about gestation, maternal health and mental health, and child development in addition to brief CBT (n=35). Duration of treatment will be eight weeks, during which participants in both groups will be assessed at the beginning (baseline; T0), weeks 3-4 (midpoint; T1), and week 8 (endpoint; T2) in order to evaluate treatment effects. We will also conduct a follow-up postnatal assessment when the child is two months of age (T3).

Inclusion and exclusion criteria

We will include pregnant women with the following characteristics: (a) aged between 16-40 years; (b) having a score of $\geq$7 on the Edinburgh Postnatal Depression Scale (EPDS); (c) gestational age between 17-26 weeks; (d) being literate; (e) owning a functional smartphone with Android for personal use. Participants will be excluded if they meet one of the following conditions: (a) pregnancies classified as being at risk (e.g., hypertension, diabetes, etc), fetal malformation, or congenital disease, (b) visual, auditory or intellectual disabilities, or chronic diseases associated with fetal development alterations, or (c) severe and/or chronic mental illness (e.g., schizophrenia, bipolar disorder).

Procedures

Recruitment and randomization

We will use social media (Facebook, Instagram) advertisements, email, and Whatsapp messages to divulge our study and recruit participants. Women interested in participating in our study will be referred to a website page where they will be provided with written information on the study's aims, procedures, and data collection. Afterwards, participants will

be required to respond to an online survey containing questions related to eligibility criteria of the study. Eligible participants will be invited to a baseline assessment which will be conducted via internet or telephone. In the baseline assessment, after obtaining informed consent, the participant will be instructed to download the Motherly and register a profile with basic information. Randomization will occur automatically in real time using PHP 7 rand function at the end of registration process [38]. After the first login the participant will already be using one of the two versions of the Motherly app (intervention or active control).

Participants cannot be blinded due to the nature of the intervention. Likewise, blinding of psychologists delivering brief CBT will not be possible. However, all assessments will be conducted by assessors blind to randomization and allocation status.

Assessments and instruments

All assessments will be conducted via the internet (videotelephony) or telephone. Assessment instruments as well as time points at which they will be used are shown in Figure 1. At baseline (T0), we will collect socio demographic information (socioeconomic status, educational level, occupation, income, etc) as well as frequency of use of smartphones, media, and apps. We will also conduct a comprehensive clinical assessment of maternal physical and mental health, perceived stress, personality traits, sleep quality, quality of life, physical activity frequency, and psychological well-being using the following instruments. We describe each instrument that will be used in the assessments below.

The Edinburgh Postnatal Depression Scale (EPDS), a 10-item scale developed to assess pre and post natal depression. It is the most used scale in studies about depression during pregnancy and the postnatal period, largely used in observational studies and clinical trials aiming to measure presence and severity of depressive symptoms. It has been validated for use in Brazil and used in multiple studies throughout the years [12, 39–41].

The Generalized Anxiety Disorder Scale (GAD-7) is a 7-item scale that assesses anxiety disorders. Because it is brief and simple, this scale is suitable in primary care, especially when the objective is to track anxiety problems in the population. This scale also allows dimensional measuring of anxiety via a continuous score, thus serving as a severity measure [42]. It has been validated in Brazil showing good psychometric properties [43].

The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) is a scale developed by the World Health Organization to assess abuse or dependence of alcohol, tobacco, and other substances (eg., cocaine, benzodiazepines, stimulants, etc) widely used in Brazil [44]. This scale allows for both dimensional and categorical assessment of problems related to substance use. We will use only the first and second items of the ASSIST scale to assess lifetime and current substance use.

The Perceived Stress Scale (PSS) is one of the most used scales in the literature to assess general symptoms of stress. This scale has 10 items assessing the individual’s perception about stress throughout the previous months using a five point Likert scale. It was previously translated to Brazilian Portuguese and validated [45]

Single-Item Measures of Personality (SIMP), a scale which assesses personality based on the Big Five theory, which proposed five types of personality: *openness to experience*, *conscientiousness*, *extraversion*, *neuroticism*, and *agreeableness*. The SIMP utilizes five descriptions designed to provide a comprehensive evaluation of desirable and undesirable aspects of each personality dimension. It is a bipolar scale, that is, each dimension has extremes (positive and negative), each with its own description. The individual assigns how much he/she fits in each bipolar dimension representing the Big Five [46]. We translated the SIMP to Brazilian Portuguese for the purpose of using in this study.

Single-item sleep quality scale (SSQS), a 1-item scale (how would you assess the quality of your sleep) demonstrating high correlation with classical scales for assessing sleep problems in the literature, such as the *Pittsburgh Sleep Quality Index* (PSQI) and the *Morning questionnaire-insomnia* (MQI). Examinees can choose from 0 to 10, indicating his/her perception of the quality of sleep (from bad to excellent) [47]. Since the SSQS was not available in Brazilian Portuguese, we translated the scale to use in the present study.

The short version of the International Physical Activity Questionnaire (IPAQ) assesses daily physical activity. Twelve countries, including Brazil, participated in the validation of this scale. The IPAQ has been shown to be equivalent to other physical activity instruments and its data has been corroborated by objective measures via accelerometer, considered the gold-standard in the literature [48]. Its robustness allowed for the assessment of physical inactivity in a study conducted in 17 countries with a sample of 130,000 participants [49].

The Ryff's Psychological Well-Being Scale, an instrument developed by Carol Ryff based on the Artistotelian construct of eudaimonia and state of the art psychological theories of happiness and well-being [50–52]. This scale assesses six dimensions that compose the state of well-being with 36 items: Positive Relations With Others, Autonomy, Environmental Mastery, Personal Growth, Purpose in Life, and Self-Acceptance. The Ryff's Psychological Well-Being Scale was validated in Brazil [53].

The *12-item health survey* (SF-12) is a short version of the SF-36, a largely utilized scale to assess quality of life associated with health outcomes. It has a Likert scale format and assesses quality of life in two-domains: physical and mental health. We used the second version of the SF-12, previously validated to the context of the Brazilian population [54].

At mid-point (T1), we will conduct a comprehensive clinical assessment of maternal physical health, and assess depression (EPDS), anxiety (GAD-7), perceived stress (PSS), and quality of sleep (SSQS), as well as prenatal and health services use.

At post-intervention (T2), 8-weeks after enrollment, we will conduct a clinical assessment with all instruments used in baseline, with the exception of the SIMP. In addition, we will administer the [55] and the Mobile App Rating Scale (MARS) [56] to assess the overall user experience of the Motherly app (intervention and active control).

At follow-up (T3), infant developmental milestones (motor, cognitive, communication/language) will be assessed when the child is two months-old using the Survey of Wellbeing of Young Children (SWYC). Common pediatric symptoms will also be assessed using the Baby Pediatric Symptom Checklist (BPSC) section of the SWYC. The SWYC was validated in Brazil [57].

All assessments will be conducted by a team of psychologists with expertise in mental health and early childhood development with previous experiences in conducting assessment in clinical trials (NCT02807870, NCT04362098). After assessments at every time point, these professionals will be required to fill questions related to the quality of interview in terms of participant's comprehension, collaboration, and quality of internet or telephone connection. Likewise, psychotherapists will fill questions related to the quality and fidelity of intervention after each session with the participant.

In addition to assessments conducted by assessors via the internet and/or telephone, we will measure depression, sleep problems, physical activity, and diet quality bi-weekly via app throughout the RCT. Assessment of symptoms of depression and anxiety will be conducted using the *Patient Health Questionnaire for Depression and Anxiety* (PHQ-4), a reduced version of the PHQ-9 [58] consisting of two questions and which has been validated in Brazil [40, 43, 59]. Sleep problems will be assessed using the Bergen *Insomnia Scale [60]*, which was developed based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [61]. The first four items assess the difficulty to initiate sleep, maintain sleep, awaken, and non-restoring sleep, and the last two assess functional impairment associated with quality of sleep. Physical activity will be evaluated daily using step counting via smartphone accelerometer, a device that measures the acceleration or force applied on the smartphone, allowing to determine the position of the smartphone on the tridimensional space. Raw data collected by the accelerometer are then converted into human steps using computational algorithms trained by means of statistical methods [62]. Thus, it is possible to assess in real time the level of physical activity of an individual in a passive and objective way. Step counting has been the most utilized method in recent studies on physical activity and sedentarism prevention [63, 64].

All instruments were already previously translated and validated in Brazil with the exception of the SIMP and SSQS. These two instruments were translated by a professional certified translator for the purposes of the current study. We plan to use data collected in our study to verify psychometric properties of these instruments, such as internal consistency and factor structure, among others.

Intervention: Motherly app + brief CBT

The intervention group will have access to Motherly 1.0, a mobile app designed to promote life habits that have been shown to improve physical and mental health in pregnant women. The Motherly 1.0 was developed by a team of psychologists, nutritionists, and app developers to translate treatment components into a mobile platform. The Motherly app was developed using the engine Unity to take advantage of enhanced graphical effects. The app consists of a package of specific and customized interventions defined by eight different

modules: 1) Mental Health; 2) Sleep; 3) Nutrition; 4) Physical activity; 5) Social support; 6) Prenatal support; 7) Postnatal support, and 8) Library of pre and postnatal content.

The aforementioned modules were integrated into a single interface (Figure 2A) using three main concepts: psychoeducation, behavior monitoring, and gaming elements. Psychoeducation is delivered in four ways: a) by tutorials explaining the rationale for the intervention and showing how to use each module; b) by psychoeducational content related to health and pregnancy delivered as brief notifications and available in a library that can be read at the users' discretion; c) by brief troubleshooting messages, which are suggestions of strategies to overcome difficulties with BA activities. Behavior monitoring is promoted using schedules, checklists, and notifications to help participants keep track of their health care visits, and schedule activities that have been associated with prevention and/or reduction of depressive symptoms. Gaming elements, defined as the use of game design elements in non-game contexts to engage users in problem-solving-behavior, are available to maintain and motivate healthy behaviors. Gaming elements are based on the psychology of motivation, behavior analysis, and game design theory [65, 66]. Specifically, the Motherly 1.0 app uses resources such as changes in the appearance of the background and icons so as to reflect participant's mood assessment (described below) and ratings of activities, and graphical and easy-to-use questionnaires for obtaining information (mood, nutritional habits). These elements, along with psychoeducational messages and user's responses act as a reinforcement for app utilization.

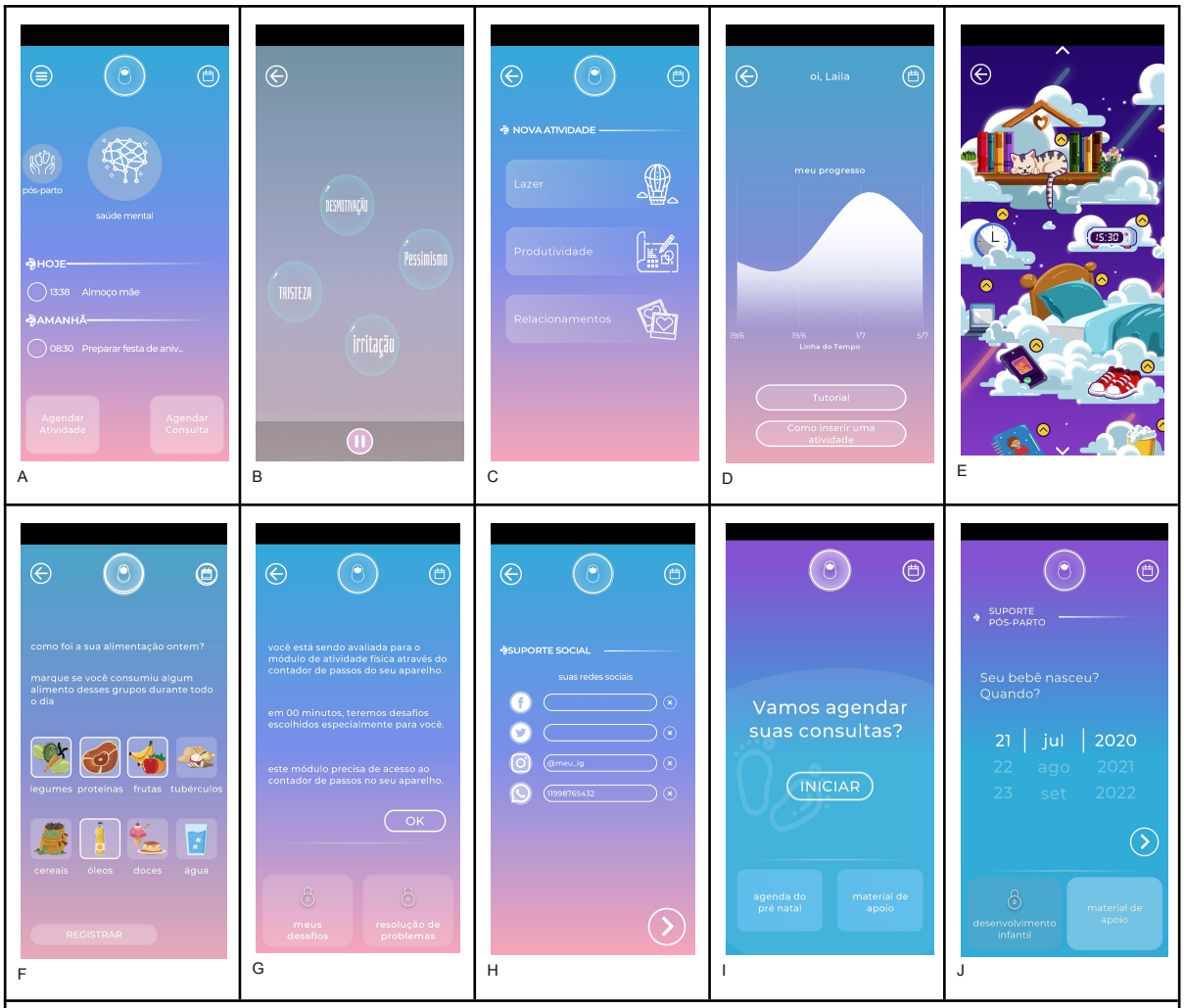

Figure 2. Screenshots of Motherly 1.0. **Figure 2A.** Main menu. **Figure 2B.** Behavioral Activation module (activities menu). **Figure 2C.** Behavioral Activation module (psychoeducation). **Figure 2D.** Behavioral monitoring. **Figure 2E.** Nutrition module. **Figure 2F.** Sleep module. **Figure 2G.** Physical activity. **Figure 2H.** Social Support. **Figure 2I**. Prenatal content. **Figure 2J**. Postnatal content.

In what follows, we provide descriptions of all modules as well as the rationale for developing them.

Mental health: this module is an adapted and automated version of Behavioral Activation (BA), a brief and structured psychological treatment based on behavioral theories of depression [67, 68]. According to these theories, depression is associated with complex interactions between individual and environmental vulnerabilities, a lack of reinforcement for nondepressed behaviors, and increased escape/avoidance behaviors that maintain depressive behaviors [69]. BA assumes that depressive symptoms might be alleviated by engaging patients in behaviors that they will ultimately find productive or pleasurable, or that might improve their life situations providing greater rewards. Therefore, BA is action-oriented and focused on problem-solving, which requires patients to test new ways of behaving in daily situations and in different areas of their lives. Specifically, BA focuses on promoting behavioral change to diminish depressive symptoms by (a) engaging patients in positively reinforced behavior (which in many cases consists in involving in activities resulting in

experiences of mastery and / or pleasure), (b) decreasing avoidance / escape behaviors that maintain depression and (c) improving problem-solving skills in order to increase access to reward and prevent depressive symptoms [69]. Decades of clinical research supports the efficacy of BA to treat depression in general populations [70–74] with some studies showing comparable effectiveness relative to antidepressant medication [75–77] or more complex forms of psychotherapy [78]. In two studies, BA has been shown to be as effective as antidepressant medication in treating depressive symptoms but with superior retention [79] or enduring effects during over a two-year follow-up [77]. Given its simplicity, BA has been successfully delivered by nonspecialists [80, 81], as well as via internet, computer, or smartphone [29, 82, 83]. In a recent RCT, BA was effective in diminishing depressive symptoms, as well as perceived stress in pregnant women [75].

Based on two manualized versions of BA [84, 85], the mental health module was designed to assist users to schedule and engage in, and monitor activities according to a plan to avoid acting exclusively according to their mood. This module consists of five basic components: (1) psychoeducation, (2) generation of activities; (3) behavior monitoring and mood assessments; (4) problem-solving; (5) reinforcement for app utilization.

(1) **Psychoeducation:** users have access to an animated video tutorial presenting the BA rationale, specifically, explaining the connections between thoughts, actions and feelings, and the ways in which they interact (Figure 2 B). Users are also shown how to use this module by means of a written tutorial. Brief psychoeducational messages are also used to provide users with information on inherent difficulties to engage in activities and common strategies to overcome them (problems-solving suggestions).

(2) **Activity scheduling:** Users can schedule activities in three main life areas: recreation, relationship, and productivity (i.e., activities related to the daily routine, career, education, and health, including activities related to other modules within Motherly, as described ahead) (Figure 2C). The app has a list of suggestions for activities that can be edited to fit the users' needs. When generating (or editing) activities, users have an option to insert a brief sentence describing a motivation to engage in that particular activity ("This activity is important to me because…"). Like the activities, the app provides an initial editable list of suggestions for motivations. The lists of suggestions for activities and motivations were developed based on the Brief Behavioral Activation Treatment for Depression: Revised Treatment Manual (BATD-R) [85] manual as well as on the clinical experience from one of the authors (PFZ) with depressive patients and aimed at increasing the likelihood that users choose activities that are actually reinforcing and objective (e.g., "buying clothes for my baby", "message my friend"), avoiding general objectives that are too hard or cannot be attained in the short term (e.g., "feeling better about myself", "be a great mother"). Therefore, activity lists contain activities that are time-limited, preferably observable by others motivations are made available so that users choose activities that are closely linked with values, ideals, or qualities they think are important. Considering the difficulty that some patients have to complete planned activities, the Motherly also has an option to insert the contact and/or name of a person that could support in completing the activity.

(3) **Activity engagement and problem solving:** Activities can be organized in a calendar. When users register activities as completed they are prompted to evaluate their sense of mastery and the difficulty to complete the activities. When participants register activities as not completed, the app provides brief troubleshooting psychoeducational messages. Specifically, participants can choose a list of reasons for not completing the activity, which will be followed by a brief and specific suggestion of strategy to overcome that difficulty. The lists of suggestions for strategies were created based on common recommendations that clinicians give patients when they face difficulties in pursuing therapeutic goals in a BA context.

(4) Mood assessments: users are prompted to report their mood bi-weekly by means of completing an abbreviated version of PHQ. Users also have the option to complete abbreviated mood assessment whenever they want.

(5) Behavior monitoring: Responses to mood assessments are available in a graph to allow users to monitor their progression. The x-axis is time and the y-axis the scores (Figure 2D). Modifications in the background colors app's icons are also used to help users to keep track of their progress.

(6) Reinforcement for module utilization: Gaming elements such as changes in the appearance of the app so as to reflect participant's mood assessment, as well as psychoeducational messages, are sent to motivate app utilization.

Sleep: this module was designed based on two techniques that are frequently part of CBT protocols for insomnia: sleep hygiene and relaxation [86]. Sleep hygiene (SH) is a psychoeducation-based intervention in which patients are provided information about lifestyle (diet, exercise, substance use), environmental (temperature, noise, light), and behavioral (e.g., the time spent lying in bed) factors that might interfere or promote better sleep [86, 87]. SH has been shown to improve sleep quality in adults with insomnia [88] and has already been shown to be effective when delivered via apps [31]. Relaxation techniques consist in procedures that decrease somatic and cognitive arousal. These procedures are especially useful for onset insomnia, since some level of arousal is present in the majority of these cases [89]. Relaxation techniques described in Motherly were based on Progressive Muscular Relaxation (PMR) and deep breathing, which have been shown to improve sleep in multisite clinical trials with pregnant women and young mothers [90, 91]. PMR involves alternately tensing and relaxing different muscle groups while patients are instructed to focus and compare feelings of relaxation and tension [92, 93]. Deep breathing aims to direct the patient's attention to breathing rhythm in order to diminish arousal [86]. Motherly users have access to sleep hygiene and relaxation procedures that are presented in the form of short audio explanations along with brief texts and visual stimuli to guide users throughout each technique (Figure 2E).

Nutrition (Figure 2F): Healthy nutrition during pregnancy is critical to maternal health and fetal development [94] and can also influence the onset of long-term diseases [95]. In addition, having good eating habits makes it easier for pregnant women to gain weight within the recommended limits [96], which is associated with better maternal and infant outcomes

[97]. Diet can also influence mental health [98, 99] and evidence suggests that increasing consumption of fruits, vegetables, legumes, whole grain cereals, healthy fats, such as nuts and seeds, and lean proteins, including fish is associated with a reduced risk for depression [100]. Therefore, the aims of the nutrition module will be to improve nutritional habits and to promote healthy gestational weight gain. The intervention includes self-monitoring, feedback feature, and push notifications. Diet and weight gain are reported by the user at baseline and every 30 days until delivery, which will be followed by tailored feedback in the form of text messages.

Information about dietary habits will be derived from a short food frequency questionnaire, consisting of 14 items developed for the study based on the current food guide for the Brazilian population [101] and the guide for pregnant women from the Brazilian Ministry of Health [102]. There are 13 food groups: total grain/cereal/roots and tubers, whole grain/cereal, vegetables, dairy products, artificial juices/soft drinks, fast-food/processed foods/salty snacks, fruits; beans, oils, nuts/seeds, fish, meat/eggs, sugar/sweets, and one item about alcoholic beverages. The questions about the frequency of consumption of these food groups will be asked regarding the week prior to assessment, and the answer options are "every day", "5-6 times per week", "2-4 times per week", "1 time per week", and "never". As no amount of alcohol is considered safe during pregnancy, pregnant women will be only asked if they had consumed alcohol in the previous week.

The feedback feature and push notifications provided are also consistent with the current food guide for the Brazilian population [101] and the guide for pregnant women from the Brazilian Ministry of Health [102]. According to these guidelines, the basis of the diet should come from fresh or minimally processed foods avoiding ultra-processed foods. Some food groups need to be consumed daily for a healthy diet (i.e., fruits, vegetables and legumes, dairy products, among others), and other food groups should be avoided (i.e., artificial juices/soft drinks, fast-food/processed foods/salty snacks, among others). Based on the recommendations aforementioned and on the answers provided, they will receive a score for each component after answering the questionnaire: (10) maximum score (reached the recommendation), (5) average score, (0) minimum score (far from reaching the recommendation). The maximum score is 140 representing 100% of adequacy. A score above 80% will be considered “good quality diet,” between 50 and 79% considered “need of some improvements” and below 50%, “need of deep improvements.” In addition to the final score, participants will also receive tailored feedback in text format for each component that did not reach the recommendation. Participants can also self-monitor food intake by answering a 24-hour food recall based on food groups whenever they wish.

Regarding gestational weight gain, participants will be asked about their pre-gestational weight and height at baseline. Pre-pregnancy body mass index (BMI) will be calculated and the recommended weight gain range will be individually provided according to the Institute of Medicine classification [103]. Weight self-monitoring consists of reporting current weight, and weight gain is presented graphically. We will also analyze gestational weight gain within the Institute of Medicine-recommended levels by using the suggested weekly gains in body weight during the second and third trimesters of pregnancy [103].

Physical activity (Figure 2G): Regular physical activity promotes several health benefits [104]. High levels of physical activity (including both recreational and non-recreational) was associated with a lower risk of mortality and cardiovascular disease events in individuals from low-income, middle-income, and high-income countries [49]. During pregnancy, an exercise program has been shown to reduce the prevalence of depression in late pregnancy and postpartum [105]. However, a recent study including 358 surveys across 168 countries (1.9 million participants) identified a global age-standardized prevalence of insufficient physical activity of 27.5% [106].

According to the American College of Obstetrician and Gynecologists (ACOG) pregnancy is an ideal time for keeping or adopting a healthy lifestyle and women with uncomplicated pregnancies are encouraged to take part in aerobic and strength-conditioning exercises before, during and after pregnancy [107]. Besides promoting benefits related to physical health outcomes of mother and child, such as reduced risk of excessive gestational weight gain, lower likelihood of gestational diabetes mellitus and lower likelihood of delivering a large-for-gestational-age infant [108], regular physical activity during pregnancy is also related to enhancing psychological well-being and may reduce the prevalence of depression in late pregnancy and postpartum [105].

The current recommendation for pregnant women is at least 20-30 minutes per day of moderate-intensity exercise every day or most days of the week (the same recommendation of at least 150 minutes per week for adults), and the exercise program should be adjusted as medically indicated [107]. Physical activity can be measured by objective monitoring using a pedometer or accelerometer. Pedometer use has been associated with increased physical activity in adults [109]. Some guidelines specifically recommend taking at least 10000 steps per day as a sufficient physical activity for adults [64].

This intervention aims to encourage physical activity by monitoring steps via accelerometer and, subsequently, propose an increase in the average number of steps by walking. First, pregnant women are informed about the recommendations and benefits of regular physical activity during pregnancy. Then, they are invited to participate in the intervention. To avoid potential harm, exclusion criteria for the module are the following: (1) multiple pregnancy; (2) those with pre-gestational BMI < 12 kg/m^2 or > 40 kg/m^2; (3) known medical or obstetric complications which restrict physical activity.

The smartphone accelerometer will be used to assess the number of daily steps. After completing the first week, users will receive feedback about their level of physical activity according to the average number of steps for the first seven days: sedentary (< 5000 daily steps), low Active (5000 - 7499 daily steps), somewhat Active (7500 - 9999 daily steps), and active (≥ 10000 daily steps) [64]. Women will be encouraged to increase their steps by 10% each week until reaching at least 10000 steps/day in a week average. Women who achieve the 10000 steps will be encouraged to continue this activity and no further increases will be proposed.

Pregnant women will be able to self-monitor their daily number of steps. At the end of each week, the weekly average of daily steps will be presented. A tailored feedback will be

provided according to the user's pre scheduled weekly step goal, and a new goal will be established for the following week. The evolution will be graphically shown. If the pregnant woman is unable to meet her goal for at least three consecutive weeks, support will be provided considering the possible reasons that may have led to this situation and some ideas to “solve” the problems will be provided. For example, if the participant select the option "*I don't know how to increase my number of steps*", an answer will be provided: “*How about starting to change small details in your daily life, such as, whenever possible, choosing stairs instead of elevator, going to nearby places on foot, extending the walk with your pet, enjoying sunny days to make pleasant walks on the street, among others."*

Social support (Figure 2H): Social support is known to be associated with morbidity and mortality [110]. During pregnancy, lack of social support is an important risk factor for maternal depression and low birth weight [111]. Interventions focused on increasing social support are known to have an effect on decreasing symptoms of depression [112]. Therefore, users will be able to make available their social media contacts in a list displayed in the app. This list can be used to contact other users.

Prenatal support (Figure 2I): In line with evidence showing that an adequate prenatal care can reduce child mortality and prevent several neonatal problems [113], Motherly provides a schedule to assist users in planning checkups from their doctors and prenatal exams according to current international guidelines [114]. Users receive notification to update their schedules, as well as register whether any health conditions have been diagnosed, thereby increasing the likelihood of making adequate prenatal care.

Postnatal support (Figure 2J): after child birth, users receive notifications describing the benefits of breastfeeding to the child development and are prompted to say whether they are able to breastfeed their babies. Mothers can register whether they are having difficulties in this, in which case the app provides a list of suggestions for solving potential breastfeeding issues.

Library of pre and postnatal content: The Motherly app has a list of educational information in the form of short articles. These articles have content related to depression and anxiety, nutrition, fetal development, breastfeeding, sleep, physical activity, among others, and can be consulted by users at their discretion.

Throughout the 8 weeks of treatment, participants in the intervention group will undergo brief CBT with a focus on BA in four sessions. More specifically, psychotherapists will help participants to use Motherly’s functionalities that were developed to implement BA, that is, schedules, activity planning, hierarchization of activities according to their level of difficulty, selection of motivations for each activity, and use of problem-solving suggestions. In addition, they will help navigate the app and use other modules. Throughout the four sessions, psychotherapists will monitor participants’ adherence, answering questions about the strategies and providing support for solving problems or circumventing barriers to completing scheduled activities. CBT techniques such as cognitive restructuring, relaxation techniques, sleep hygiene, stress and anxiety management, among other evidence-based techniques might be used if appropriate to treat depression and possible comorbidities. The

general structure of the sessions will be based on a guide developed by the authors (DF and PFZ) to help psychotherapists select CBT interventions that are adequate for each participant.

Active control: Educational app + brief online CBT

Participants allocated to the active control group will have access to a simplified version of the app consisting of educational content about various aspects of pregnancy, maternal physical and mental health, and child development. Active intervention functionalities, such as behavioral activation, activity scheduling, sleep hygiene, among others, will not be present in this simplified version. As with the intervention group, participants from the active control group will receive app notifications to answer questions related to the outcomes of this study. The active control group will also receive four sessions of brief CBT throughout the 8 weeks, with a focus on BA. They will be guided by psychotherapists to plan, schedule, and engage in positively reinforcing activities, and will be aided to develop problem-solving strategies for circumventing barriers to completing scheduled activities. However, implementation of these techniques will be conducted without the aid of the Motherly app (as these functionalities are not present in the active control app). Throughout the four sessions, psychotherapists will monitor participants' adherence, answering questions about the strategies and providing support for solving problems or CBT techniques, such as cognitive restructuring, relaxation techniques, sleep hygiene, stress and anxiety management, among other evidence-based techniques might be used if appropriate to the case. The structure of the sessions will also follow the guide mentioned previously.

Sample Size

We calculated the sample size based on an expected effect size of 0.65 on depressive symptoms, which is based on a previous meta-analysis [115] (difference in means between two independent groups) considering a probability of type I error of 5%, statistical power of 80%, a two-tailed test, and a dropout rate of 15%.

Statistical analyses

First, continuous variables will be described using central tendency measures and categorical variables will be described using frequencies and cross tabulations. To analyze the potential impact of the intervention on depression symptoms we will use an intention-to-treat (ITT) approach. To perform ITT analyses, we will use multiple imputation by chained equations to include every participant randomized. The effects of intervention on maternal depression (primary outcome) and secondary outcomes will be tested using a generalized linear mixed model for longitudinal data. Estimated marginal means will be extracted from these models to describe primary and secondary outcomes of the study for both groups. Marginal means will be used to plot data. Additionally, we will investigate the potential role of moderators (baseline characteristics, such as socioeconomic aspects and personality traits) of the treatment effect on outcomes using a regression-based approach [116]. Standardized effect sizes will be calculated from the difference between group means using criteria described by Cohen [117]. Tests will be considered significant at $p<0.05$ and

95% confidence intervals will be reported for all parameters. All analyses will be conducted using STATA 16 and R.

Data safety

All data from the assessments as well as clinical records from CBT sessions will be entered electronically via Research Electronic Data Capture (REDCap) [118], thereby ensuring safety of the data and protections of participants' information.

Staff

All assessments will be conducted by a team of psychologists with expertise in mental health and early childhood development with experience in clinical trials. Assessors will receive training sessions with a focus on presenting study details, as well as in-depth explanations of all instruments used. Brief CBT will be delivered by female psychologists with a certified specialization in CBT and previous experience in treating depression. In order to ensure fidelity and quality of treatment, psychotherapists will receive weekly supervision by a senior doctorate level clinical psychologist (PFZ) with clinical background in CBT and BA.

Ethical issues and dissemination

Given that the intervention in this study is non-invasive, the risk for participants can be considered marginal. Participants will be informed that questions in the assessment protocol might cause some level of subjective discomfort, but that they are not obliged to answer them and will still continue in the study. Irrespective of the group to which participants will be allocated, they will benefit from receiving brief CBT by a mental health expert, which can potentially alleviate symptoms of depression or anxiety.

Throughout the study, both intervention and active control groups will be assessed for symptoms of depression, anxiety, sleep, and dietary patterns via app. These data will be available to researchers in real time for monitoring purposes if participants need to be referred to specialized care due to severe symptoms of depression or suicidal ideation. In these cases, participants will be contacted by internet or telephone.

During treatment, participants will be referred to specialized care in case depression symptoms worsen to serious, with suicidal ideation, functional impairment, appearance of psychotic symptoms, among others. Participants presenting mental health issues associated with the COVID-19 pandemic and/or social distancing will be treated with psychological first care techniques adequate to stress-related symptomatology due to adverse conditions [119]. At the end of 8 weeks, participants who do not show remission of symptoms of depression will be referred to specialized mental health services.

This study has been approved by the ethics committee of the University of Sao Paulo Medical School (reference number: 3371750). All participants will be required to provide informed consent. In cases where participants are under age, legal guardians will be required to sign informed consent after participants agree to participate in the study.

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