Research project

Official title : Starting before birth to prevent maternal mental health problems: "Parents and Babies" program (Programme "Toi, Moi, Bébé")

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RESEARCH PROJECT

Starting before birth to prevent maternal mental health problems: "Parents and Babies" program (Programme "*Toi, Moi, Bébé*")

PRINCIPAL INVESTIGATOR:

Dre Sylvana Côté: Overall trial management and proper intervention implementation
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CO-INVESTIGATORS/COLLABORATORS:

1. Dr. Cindy-Lee Dennis, Professor, Faculty of Nursing and the Faculty of Medicine, University of Toronto: Expert in randomized controlled trial in the perinatal population. She is advisor for the substantive, methodological, and logistic aspects of the design and execution of the study.
2. Dr Benoit Mâsse, Professor, School of Public Health, University of Montreal: Senior biostatistician and expert in clinical trial design and data management analysis. He is Director of the Applied Clinical Research Unit (URCA) and will oversee all statistical aspects of this trial.
3. Dr. Anick Bérard, Professor, Faculty of Pharmacy, University of Montreal: Epidemiologist with extensive experience in maternal depression and conducting studies using data linkage and social media recruitment. She will work with the NPIs to oversee recruitment and linkage.
4. Dr. Catherine Haeck: Economist responsible for the economic evaluation.
5. Dr Lucie Morin, Chief Obstetric at the CHU Sainte-Justine: Provides administrative and logistical support for the realization of the trial at the CHU Sainte-Justine. Oversees the safety procedures together with Dr Amirali and Saint-André,
6. Drs. Martin Saint André, Medical Chief of the Pediatric Psychiatry Clinic, CHU Sainte-Justine: Perinatal psychiatrist involved in the design and monitoring of the intervention. Together with Tina Montreuil and Lila Amirali, they have produced the intervention material and conceptualized the trial. They will provide training and supervision, building on their extensive clinical expertise, and will be heading the knowledge transfer plan to the clinical community.
7. Dr. Tina Montreuil, Assistant Professor, Department of Educational and Counselling Psychology, McGill University: Psychologist involved in the design and monitoring of the intervention.
8. Dr. Lila Amirali, Chief of the Psychiatry Department, CHU Sainte-Justine: Psychiatrist involved in the design and monitoring of the intervention.
9. Dr. Isabelle Boucoiran, gynecologist, CHU Sainte-Justine: Involved in the design of the intervention.
10. Dr Kieran O'Donnell, Professor, Department of Psychiatry, McGill University: Expert in observational studies on perinatal mental health. Involved in the design of the intervention and the conceptualization of the research trial.
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12. Dr. Linda Booij, Professor, Department of Psychology, University Concordia: Involved in the design of the intervention and the conceptualization of the research trial.

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14. Mrs. Julie Béland, Clinical Nurse Counsellor, CHU Sainte-Justine: Involved in the design, coordination and implementation of the intervention.
15. Mrs, Valérie Samson, Clinical Nurse Counsellor, CHU Sainte-Justine: Involved in the coordination and the implementation of the pilot study.
16. Mrs. Myriam Clement, PhD Student, School of Public Health, University of Montreal: Involved in the design, coordination and implementation of the intervention.

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Context

During pregnancy and the postpartum period, women are at heightened risk of mental health problems, with 1/5 experiencing moderate to high levels of depressive symptoms (1, 2). Perinatal mental health problems often go unrecognized and undiagnosed (3), with fewer than 20% of symptomatic women receiving treatment (4). The cost of untreated maternal depression is estimated at over $17,000 US per mother per year over the first five years of the child's life. In comparison, gestational diabetes costs up to $3,300 per mother and occurs only during pregnancy (5). The consequences of untreated perinatal mood disorders include maternal psychological, social, occupational, and physical dysfunction (1, 2).

About 20-25% of pregnant women have subclinical levels of depression (Edinburgh Postnatal Depression Scale (EPDS) score 9-12) and 2/3 of these will go on to clinical postpartum depression (EPDS $\geq$ 13) (6-8). Though ineligible for publicly funded clinical services, these women have poorer parenting/offspring outcomes (6). Fifteen meta-analyses (300+ studies) have documented associations between maternal depression and poor cognitive, behavioral, and emotional outcomes in the offspring, starting at birth and extending into adolescence (9-18). Preventive interventions and childhood assessments could inform the putatively causal role of maternal mental health on child development. In this study, we test an early pregnancy intervention and its impact on postpartum ages 3 and 6 months. The virtual or remote format of the intervention (online and telephone) is designed to overcome long-standing mental health management barriers.

Prevention of Postpartum Issues

There is growing evidence that the societal burden of perinatal mental health issues can be prevented. Most women with postpartum depression have symptoms during pregnancy (19, 20). High-risk women may be identified by simple screening (e.g., mobile phone) and EPDS (21), and prevention programs in person or in groups are effective (2). Recognizing potential for early prevention, the United States Preventive Services Task Force (2019) issued a level B recommendation "that clinicians provide or refer people who are at increased risk of perinatal depression to counseling interventions." These include cognitive behavioral therapy (CBT) and interpersonal counseling, such as the existing, evidence-based *Mothers & Babies* program (22-25).

One important advantage of psychosocial support initiated before birth among high-risk women is reducing the allostatic load, or the wear and tear on the body, generated by stress and mental health symptoms. Allostatic load increases as pregnant women prepare themselves for the heavy emotional and physical demands of giving birth and parenting (26). In Canada, we lack a comprehensive perinatal prevention mental health framework. Existing research and policy have focused on postpartum depression; we have not addressed prevention in the antenatal period.

Efficacy of Virtual Interventions

Counseling is the treatment of choice for pregnant women with moderate levels of depression. Evidence suggests effectiveness and no documented risks (2). Importantly, evidence is low for the efficacy of antidepressant drugs in pregnant women when used as sole treatment for moderate levels of depression. Further, a number of studies have raised concerns about the potential risks of fetal exposure to antidepressants (27-33). Despite the fact that women prefer counseling over medication (34), fewer than 20% of women with perinatal depression receive counseling (4).

Barriers to counseling include lack of accessible and affordable programs (35), stigma related to mental health problems (36, 37), cost and time constraints related to transportation

to appointments, challenges of finding childcare while attending treatment (37), and geographical barriers in under-served rural or socioeconomically disadvantaged areas (34). Since the start of the COVID-19 pandemic in March 2020, social distancing, mandatory mask-wearing, and other public health measures have added to the complexities of in-person treatment, while the rates of depression in pregnant women have increased 2-3 fold (38, 39). There is a pressing need for evidence of the efficacy of remote prevention and treatment modalities.

Remote, or virtual, care is a promising solution to long-standing barriers to effective management of perinatal mental disorders (34). Virtual care is defined as any interaction occurring between patients and health care professionals using communication technology. Previous studies have also suggested that patients and clinicians are satisfied with virtual modalities (including psychiatric treatment by telephone) and that remote therapy can lead to improved clinical outcomes (40). Almost 80% of pregnant women would consider computer-based applications, because the material is accessible anytime, anywhere, no trip to a therapist's office is required, and feelings are more comfortably reported in a virtual setting (41). Women of reproductive age commonly use the internet, social media, and smartphone apps. There is accumulated evidence of the effectiveness of digital intervention in this population (34, 42). Importantly, qualitative data from our pilot study showed high levels of acceptability and satisfaction to virtual care and interventions (**Appendix A**).

There is, however, a paucity of studies providing evidence for the effectiveness of antenatal virtual prevention programs for postpartum issues. A systematic review including 4 randomized controlled trials (RCTs) for the digital treatment of postpartum depression identified small-to-medium effect sizes (43), but none of these interventions were initiated during pregnancy (43, 44). In another small RCT conducted in pregnancy (n = 42), Forsell et al. (2017) found that participants who received pregnancy-adapted internet-based CBT had reduced rates of clinical depression after the 10-week intervention. In one large Norwegian trial (n = 1342), Haga et al. (2019) showed the efficacy of internet-based CBT for maternal depression up to 6 weeks after birth. This impact, however, was not maintained at the 3- and 6-month follow-up. Loss of effect may be explained by high attrition rates related to the fully automated format (no personal contact). It is important to note that virtual interventions with personal (e.g., telephone, text, email) contact have higher retention rates than those without (34), underlining the need for individual support in addition to a web-based modality. In our pilot project, telephone follow-up was rated as "essential" in 40% of cases and "very useful" in 40% of cases. To summarize, there is preliminary evidence suggesting that virtual interventions during pregnancy may be effective in preventing postpartum depression. However, we need data on longer-term effectiveness using larger samples of women most at-risk of postpartum depression, i.e., those with subclinical to moderate levels of depression in pregnancy.

Partner-Inclusive Intervention

Previous studies for the prevention of maternal depression have not explicitly included the partner. Yet perceived lack of partner support is strongly associated with maternal stress (45) and depressive symptom severity (46). Several recommendations have been made to improve the level of couple satisfaction and reciprocal support (47) but few studies targeting perinatal maternal depression have included partners. In one notable exception, a study in China showed that CBT for couples was more effective in reducing the incidence of postpartum depression than maternal therapy alone (48). Given the importance of partners in maternal mental health, greater consideration should be given to partner well-being and the role they play in bolstering or aggravating perinatal depression (47). Allocating more resources and introducing family-focused care with depression screening in

early pregnancy is recognized as critical for both parents but rarely addressed (49). This trial will test the efficacy of an intervention in which partners are encouraged to take part and engage in sessions that are specifically designed for the mother-partner dyad.

Causal Role of Maternal Mental Health in Child Development

Studies showing associations between perinatal maternal health and child development are summarized in 15 meta-analyses (17, 18). Small to moderate negative effect sizes are reported in cognitive development and in internalizing and externalizing problems in childhood, extending into adolescence (18). This body of research is based on correlational association studies, and as such, precludes any conclusion about the causal role of maternal depression in child development. RCTs on the treatment of maternal mental health problems seldom assess the impact on the child. This knowledge, however, is crucial to developing preventive interventions to be implemented early in pregnancy. Pediatricians and child development specialists need to know whether addressing early (subclinical) maternal mental health issues in pregnancy is a strategy that can benefit children long-term. The putative role of maternal mental health in child development can be evaluated in clinical trials that include child outcomes for sufficiently long follow-ups.

Research Questions

Primary research question: Compared to a fully automated virtual (with a workbook or online material) intervention, what is the effect of the virtual intervention with telephone support for pregnant women with subclinical depressive symptoms on maternal depression at 3 months' postpartum? We adopted an indicated prevention strategy (targeted or secondary prevention), targeting women with symptoms of depression during pregnancy.

Secondary research questions: Compared to a fully automated virtual (with a workbook or online material) intervention, what is the effect of the virtual intervention with telephone support on: 1) maternal depression at 6 months' postpartum; 2) maternal anxiety, perceived stress, well-being, self-efficacy, self-compassion, sleep quality, tobacco, alcohol and drug usage, social functioning, social support, marital satisfaction, co-parenting and parental cognitions and practices, at 3 and 6 months' postpartum; 3) child's socioemotional development at ages 3 and 6 months; 4) maternal health care services utilization at 6 months' postpartum.

Tertiary research questions: What is the effect of a virtual intervention (with a workbook or online material) + telephone support on 1) partner depression, anxiety, perceived stress, well-being, self-efficacy, self-compassion, sleep quality, tobacco, alcohol and drug usage, social functioning, social support, marital satisfaction, co-parenting and parental cognitions and practices, at 3 and 6 months' postpartum; 2) What are the moderators of the effect (e.g., compliance to the intervention, COVID-19 infection of self or relatives, personality disorder traits, socioeconomic level, ethnicity, gender at the baseline, and sex of the child).

Method

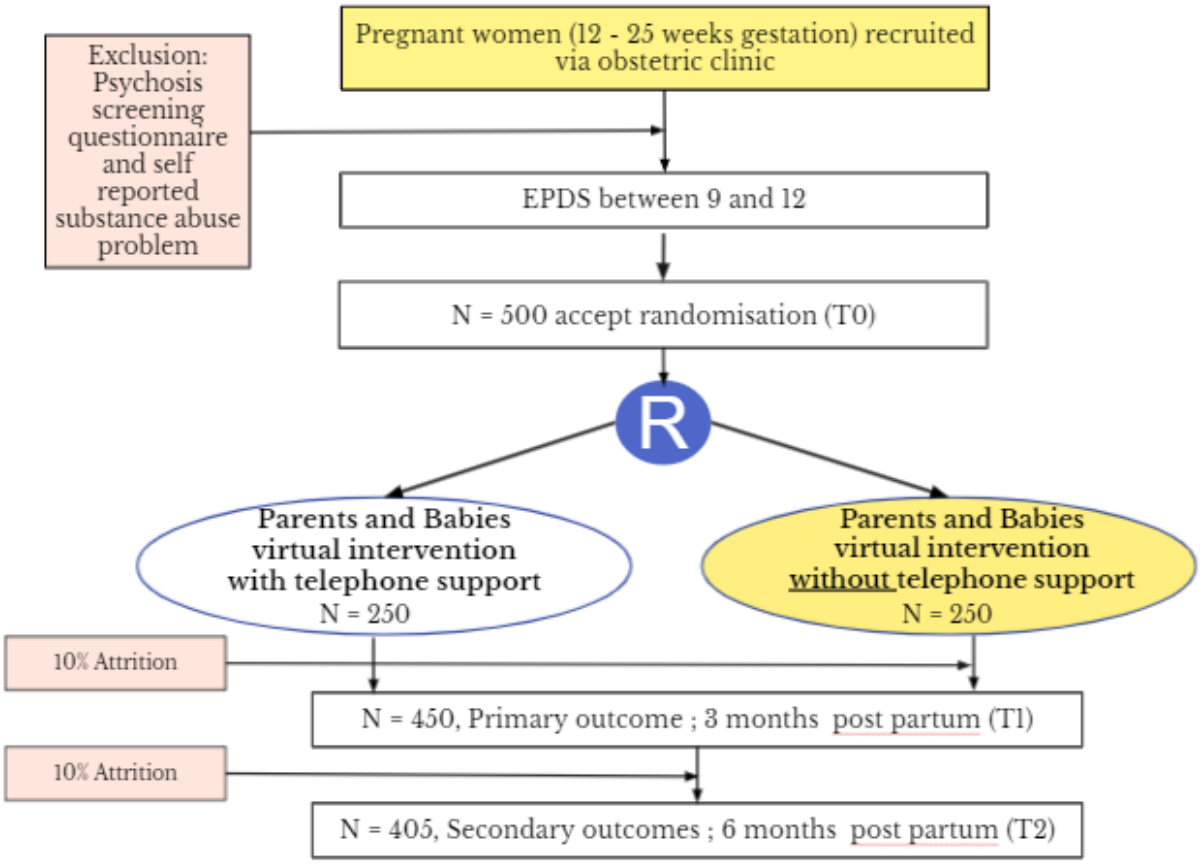
Design

A randomized controlled trial (RCT) of 500 Quebec women with a 1:1 assignment to either virtual preventive intervention with telephone support or without telephone support (control). Figure 1 presents the trial design.

Population

French-speaking pregnant women older than 14 years old, with subclinical levels of depression (EPSD 9-12).

Figure 1. Trial design



Pregnant Women Recruitment

Pregnant women will be recruited via three possible means: 1) Recruitment posters and pamphlets (Appendix B, Recruitment poster and pamphlet) distributed in clinics associated with the CHU Ste Justine; 2) Obstetrician, psychiatrists or general practitioner in clinics associated with the CHU Ste Justine; or 3) Advertisements posted on various social media (Facebook, Instagram; Twitter, etc.). Interested women will either 1) connect to a web page and fill a contact form (Appendix C); or 2) contact us by phone, text message or email.

The research coordinator will contact women referred by practitioners or through advertisement. The study will be explained and a consent form (Appendix F, Consent forms) will then be sent through REDCap. Participants will sign virtually. Then, they will respond by telephone to the eligibility questionnaire (5 min.), including the EPDS (50) psychosis screening questionnaire and self reported substance abuse problem. Those with subclinical levels of depression (EPDS 9-12) and without psychosis and substance abuse problem will be randomized via REDCap and informed of their group allocation.

Partners Recruitment

During the recruitment phone call with pregnant women, the research coordinator will explain the possibility of partners to participate in the study and the advantage of it. A partner can be the spouse or any other significant person who will accompany the pregnant woman during pregnancy and after childbirth. It is recommended to keep the same person for the duration of the course. The research coordinator will ask the pregnant women to identify her partner and if he or she is at home at this moment, he or she will be invited to join the call. Partners will be eligible only if the pregnant woman signed the consent form and is eligible for the study. If the partner is absent, the research coordinator will ask for his or her email or telephone number. If the pregnant woman sign the consent form and is eligible for the study, an invitation will be sent to briefly explain the project and to ask them if they accept us to call them to give more information and recruit them if interested. The research coordinator will then contact those interested, explain the study and send an email with the consent form.

Recruited pregnant women and partners will receive a notification with a link to answer the baseline questionnaire (Appendix E, Baseline and follow-up questionnaires) online and our contact information to take an appointment with a research assistant if they prefer to answer the questionnaire on the phone. After completion of the baseline questionnaire, access to the intervention website will be authorized.

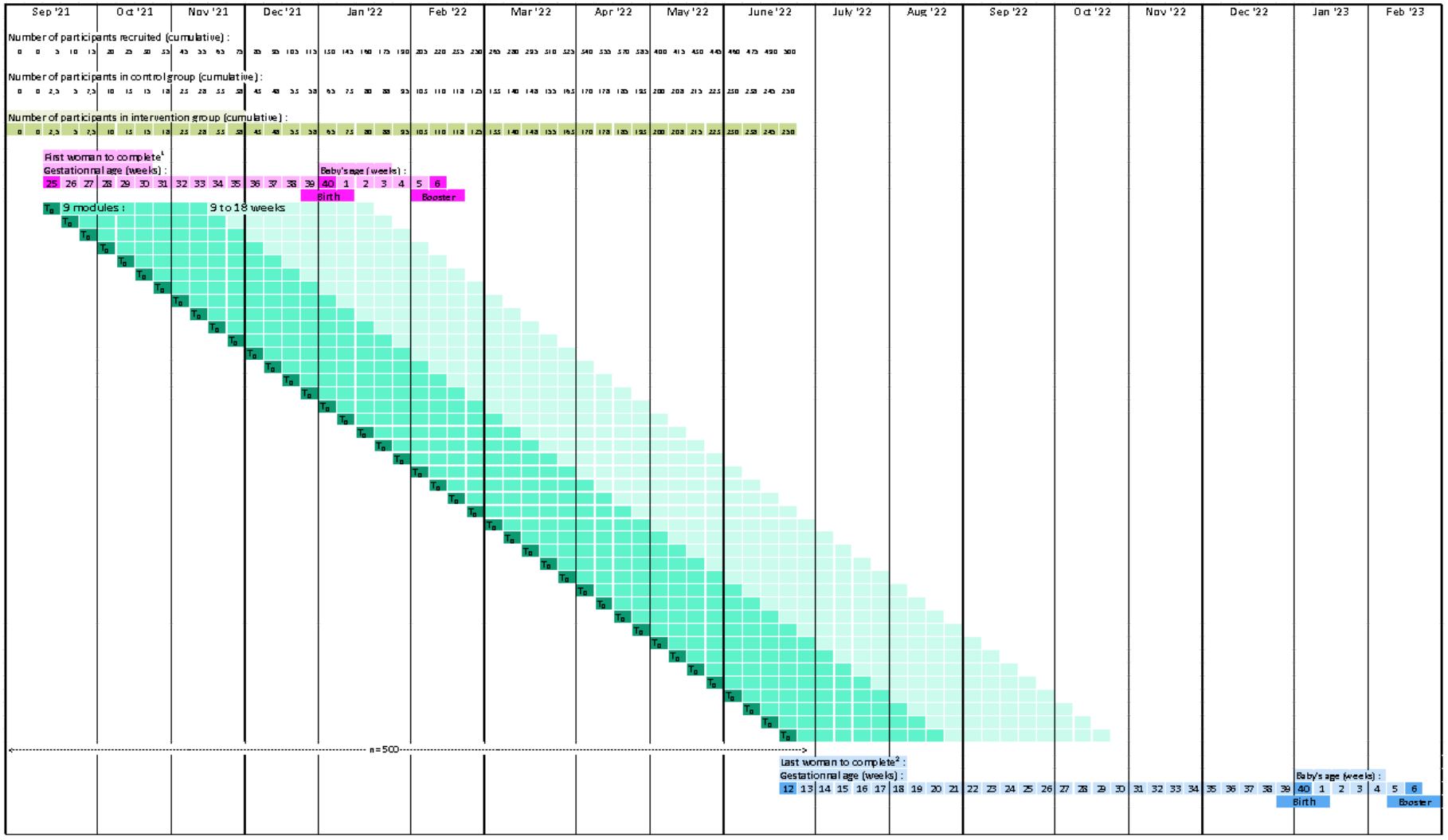
Planned recruitment rate

The participant recruitment rate depends on two factors: 1) capacity to recruit pregnant women with subclinical depressive symptoms (EPDS 9-12); 2) participant acceptance of the trial. In one of our ongoing mental health studies in pregnant women, 374 (22.1%) participants with EPDS scores 9-12 (out of 1695 assessed) were recruited over social media in a two-week period (i.e., 185/week). Within Sainte Justine's obstetrics clinics, 25 – 30 women/week are assessed with the EPDS. Therefore, we expect to recruit around five women/week at the beginning of our trial. When we will expand our recruitment on social media, we estimate to recruit n = 15 women per week willing to accept randomization. The recruitment period should last a total of approximately ten months. Thus, an average of 25 women per month would enter the intervention under the guidance of one of 3 *coaches* (i.e., 8 women/*coach*). Intervention activities will take 18-20 months. Figure 2 presents the schedule of recruitment and intervention implementation.

Participating centers.

The trial is based at Sainte Justine Hospital (CHU Ste-Justine), the largest mother-child hospital in Quebec. Affiliated obstetric clinics will refer patients to the study site (Appendix G, Letters of Support). These clinics provide an ideal setting for recruiting mothers of diverse ethnic backgrounds.

Figure 2. Schedule of recruitment and intervention implementation



[1] First women to complete will begin the trial at 25 gestational weeks in the first wave of recruitment
[2] Last women to complete will begin the trial at 12 gestational weeks in the last wave of recruitment

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Sample

We followed the USPSTF recommendation for the prevention of postpartum depression (2) by targeting pregnant women with moderate depressive symptoms, who could reasonably be considered as signaling distress or early signs of illness, are at high risk for postpartum depression, and are not eligible for specialized psychiatric care. Our program is a virtual and population-based preventive intervention, not a treatment for clinical depression, although it could reasonably be conceived as an adjuvant to psychiatric care.

Pregnant women inclusion criteria: Pregnant women (12-25 weeks' gestation), ages 14 years or older, with: 1) subclinical levels of depression (EPDS scores 9-12) and 2) ability to read and understand French.

Pregnant women exclusion criteria: 1) EPDS score in the clinical range (≥ 13) or no symptoms (EPDS < 9); 2) Positive screening of psychotic symptoms using the Psychosis Screening Questionnaire (PSQ); 3) self-reported substance abuse problems. These criteria are consistent with those of other prevention trials (51).

Partners inclusion criteria: 1) The spouse or any other significant person who will accompany the pregnant woman during pregnancy and after childbirth, chosen by the pregnant woman. 2) The pregnant woman has consented to participate in the study.

Participant allocation. Randomization will be centrally controlled by the CHU Ste-Justine Applied Clinical Research Unit (URCA), headed by co-PI Benoît Mâsse. An independent biostatistician will create the randomization scheme, a computer-generated random listing using a 1:1 allocation, according to trial statistician instructions. Random permuted blocks randomization will be used. The randomization list will be WEB-based and completed via REDCap.

Bias protection. With detailed informed consent procedures, it is expected that pregnant women will accept their randomized group allocation. The intervention team will be blinded to the initial level of depressive symptoms. No formal virtual depression prevention intervention program yet exists in Quebec. There will be no interference with usual medical/nursing care, which may include antidepressant medication and/or psychotherapy.

Sample size. A meta-analysis of 58 studies indicates that the overall prevalence of postpartum depression is 17% (95% CI: 0.15–0.20) (53). This estimate falls within previously published estimates of 13%–19.2% (54, 55) and is similar to Hahn-Holbrook's 2018 finding of 17.7%. In-person interventions using the *Mother & Babies* course reported moderate effect sizes (OR = 0.28 (0.08-0.94) (22) and OR = 0.45 (0.19-1.10) (24)). Fully web-based without nurse-based telephone support reported small to moderate effect sizes (40). Given that the proposed intervention is offered virtually with nurse-based telephone support, we calculated a sample size that allows us to detect a moderate decrease in rates of clinical depression. We anticipate that 20% of pregnant women in the control group will have an EPDS score ≥ 13 at postpartum. A total of 500 pregnant women (250 per arm) is needed to detect an absolute reduction of 10% (i.e., 20% of women with EPDS ≥ 13 in the control arm versus 10% in the intervention arm) with 80% of power and a 2-tailed alpha of 5%. The sample size includes an attrition rate of 10% for 3 months' postpartum and another 10% between 3 and 6 months' postpartum. Based on our experience with pregnant women and the intervention (see Section about Pilot Study), the 10% attrition estimate is conservative. As most of the secondary

outcomes are continuous, the sample size provides enough power to detect small to moderate effect sizes using a 2-tailed alpha of 1% to account for multiple tests.

Compliance. We conducted a feasibility pilot study including 17 pregnant women. All began to read the online material and 2 refused further participation after 2 telephone calls, a dropout rate of 11.7%. We therefore expect that 80-90% of the intervention group will read at least some of the intervention material. Intervention compliance will be defined as completion of a minimum of 6/8 online modules and 6/10 telephone follow-ups. Compliance will be monitored automatically online and by nurses during telephone calls. Weekly text reminders will be sent out to maximize compliance (see details in Appendix H).

Loss to follow up. The following proactive telephone strategies will be employed to encourage retention. Each computer-based questionnaire will contain a contact form for the research nurse to record the date, time of the call, the status of calls (busy, call back, no answer, etc.), email address, name and contact information of the partner and of one additional reference person (e.g., family member). Participants will be telephoned during their stated "best time to contact" period. Congratulations cards will be sent at the birth of the child, showing contact information for the study. Participants will be invited to go to the study Facebook page, with periodic lotteries of gift certificates. Additional strategies to ensure a high retention rate, based on a Cochrane review (56), include card pre-notification of impending interview and a small token of appreciation for each assessment completed. All these strategies have been successfully used in Dennis' postpartum depression prevention trial with good results (retention rate = 87% of the 12-week assessment and 85% of the 24-week assessment).

Description of " Parents and Babies" (« *Toi, Moi, Bébé* ») intervention

The ***Parents & Babies*** intervention to be evaluated is an adaptation of the existing, evidence-based *Mothers & Babies* program (see Authorship Rights, Appendix I), which has shown efficacy in four clinical trials for the prevention of postpartum depression through in-person (group or individual) counseling (22-25). In a study with a low uptake of the intervention, a Spanish web-based format without telephone contact was tested and suggested some impact on women with moderately high levels of depression (57).

The *Parents & Babies* program was adapted to be virtual and include: 1) specific modules for the mother-partner dyad; 2) third-wave cognitive behavioral therapy (CBT) strategies targeting well-being, relaxation, mindfulness, self-compassion, and gratitude; 3) confinement and social distancing related material. Participants follow the program online or with a paper workbook and are called weekly by a member of the intervention team. We started a pilot study in July 2020 (n=17) to examine the feasibility and acceptability and results thus far suggest high satisfaction and compliance (Appendix A). We tested assessment protocols within two maternal mental health observational studies across Canada led by our co-applicants (58, 59). We therefore have the capacity to set up the larger proposed trial within an efficient timeframe and to implement within one month after the Ethics Committee approval.

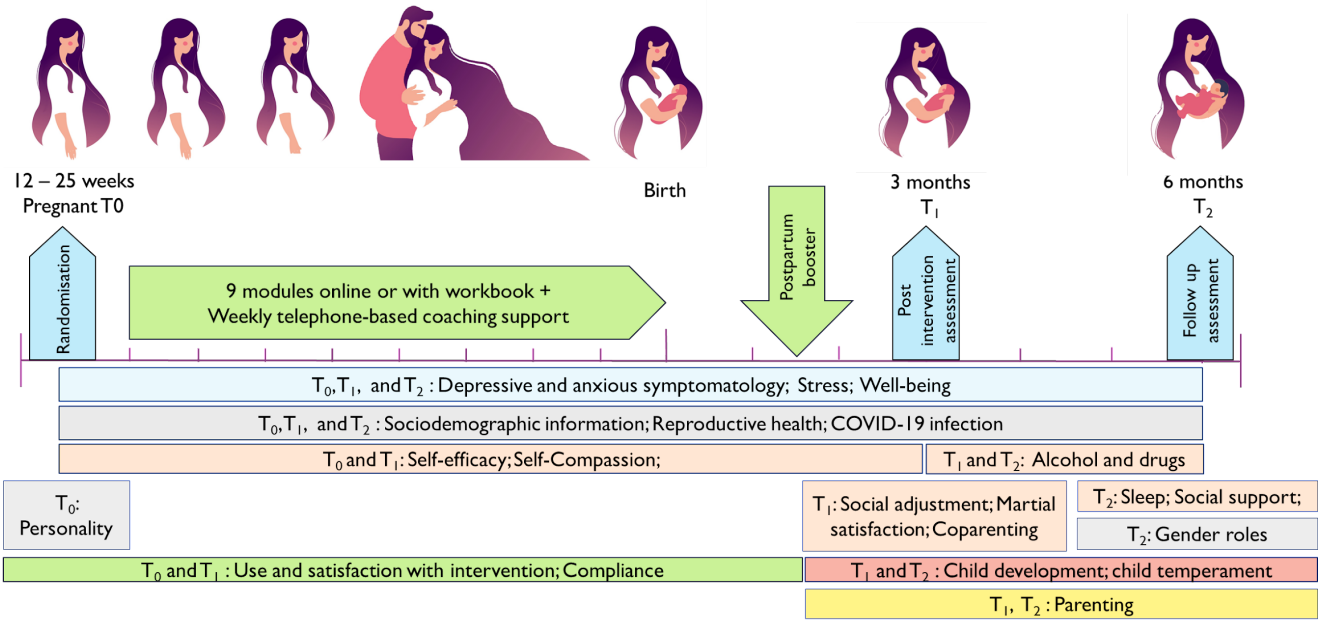
The *Parents & Babies* intervention consists of 1) a self-help web-based platform and workbook of 10 modules offering CBT intervention and exercises; and 2) 10 telephone counseling calls by trained coaches: 9 during pregnancy (one call/week) and 1 at 6 weeks postpartum. Each web module takes 10-20 minutes online; one module per 1 or 2 weeks is advised. The program focuses on pleasant and rewarding activities, recognizing and distinguishing between harmful and beneficial thoughts, reducing cognitive distortions and automatic thoughts, encouraging social networking and healthy communication, promotion of

a positive coparenting relationship and mother-child attachment (See Appendix J for access to the intervention website). Further, it proposes relaxation and mindfulness exercises. We have included individual telephone calls by a trained coaches aimed to: 1) encourage the use of online material; 2) identify strategies for overcoming obstacles; 3) help apply content to real-life settings; and 4) underscore the participants' success in using effective coping strategies (see Appendix K, Coaching phone calls guide).

Partner participation. Women are encouraged to involve their partner if they feel it is appropriate. Partners are invited to specific modules.

Duration of treatment period. The typical duration of the program is 2 months (8 weeks) during pregnancy and 2 months over the first 3 months of the baby's life. The two postpartum sessions aim to lend support during the challenges of the postpartum period. The proposed frequency of nurse telephone follow-up is once/week in pregnancy and once/month in postpartum, but this can be adapted to the needs of the woman and/or her partner. Figure 3 presents the intervention and assessments.

Figure 3. Frequency and duration of the follow-up



Participants will fill out questionnaires (online or by telephone) at T_0 (12-25 weeks' gestation), T_1 (3 months' postpartum), and T_2 (6-months postpartum) to assess baseline values and trial outcomes, respectively. If we show efficacy at 3 months' postpartum (primary outcome), we will seek funding to follow families over the early childhood years. Real date of birth will be assessed six weeks after the estimated date of birth.

Coaches training and supervision. PhD students in clinical psychology and Master's students in nursing are ideally suited to conduct the 10 follow-up calls. They will be supervised by our multidisciplinary team (2 nurses, 2 clinical psychologists, and 2 psychiatrists). All coaches will receive 5-day training in perinatal mental health and use of the intervention material. Procedures for calls will be outlined in the intervention manual. The supervision team will oversee implementation as part of the Executive Committee. Intervention sessions will be audiotaped and randomly reviewed by the supervision team to ensure compliance with the material.

Virtual intervention without telephone support (control group). The control group will receive a fully automated version of the virtual intervention

Data Collection

We will conduct a comprehensive assessment of perinatal maternal mental health and functioning as well as factors that may modify the impact of the intervention. The chosen assessment tools are validated (French and English), require low levels of literacy and take only 15-30 minutes to complete (Appendix L, Description of assessment tools). They have been used previously with pregnant women and examined for clarity, comprehension, and ease of use. The questionnaires will be completed online via REDCap or over the telephone with a research assistant blinded to group allocation depending on maternal preference, and with the partner if the woman so chooses.

Primary outcome. Maternal depression at 3 months' postpartum was chosen as the primary outcome to: 1) ensure comparability to other perinatal trials (60-67) and 2) to reduce potential biases induced by attrition. The primary outcome will be the proportion of women with EPDS scores above the clinical cut-off for depression (EPDS $\geq$ 13)). Differences between experimental and control groups will be analyzed at T_1 (3 months' postpartum) and again at T_2 (6 months' postpartum, secondary outcomes). The EPDS is an internationally recommended 10-item self-report scale that assesses depressive symptoms on a 4-point scale; scores range from 0 to 30 with higher scores representing higher symptomatology. More than 80% of perinatal depression studies use self-report measures (73) and the majority use the EPDS. The EPDS was created to counter the limitations of other well-established depression scales when used during the perinatal period. It has been validated by standardized psychiatric interviews with large sample sizes and has well-documented reliability and validity of over 11 languages (50, 74). Participants will fill out the EPDS at 3 assessment times: baseline (T_0, as part of inclusion criterion), T_1, and T_2.

Secondary outcomes. Participant and partner assessments at baseline, T_1 and T_2. The proposed intervention is based on CBT principles used to treat both anxiety and depression. As anxiety is highly correlated with perinatal depression, it is an important secondary outcome. ***Generalized anxiety***. The proposed intervention is based on CBT principles used to treat both anxiety and depression. As anxiety is highly correlated with perinatal depression, it is an important secondary outcome. Anxiety will be assessed at all 3 time points, using the Generalized Anxiety Disorder 7-item (GAD-7) scale, an extensively validated self-report instrument (75-77). ***Anxiety related to pregnancy*** will be measured with the 10-item Pregnancy-specific anxiety scale (PRAQ-R2) (78, 79) at baseline. ***Stress*** will be assessed using the 10-item form of the Perceived Stress Scale, at six months postpartum (80, 81). ***Well Being*** will be evaluated with the 5-item WHO-5 well-being index at T_1 (82). ***Self-efficacy*** will be assessed using the 10-item General Self-Efficacy Scale (GSE) at 3 months postpartum (83, 84). ***Self-Compassion*** will be measured with the 12-item shortened version of the Self-Compassion Scale (SCS) (85-87), at 3 months postpartum. ***Sleep.*** Sleep may improve as a result of the increased capacity for relaxation, mindfulness, and emotional regulation fostered by the intervention. At 3 months postpartum, we will assess sleep quality, a critical aspect of perinatal maternal health, using the 19-item Pittsburgh Sleep Quality Index (PSQI) (88, 89), a self-report over a one-month interval with very good psychometric properties and validated for use during postpartum (90). ***Tobacco, alcohol and drug use*** will be self-reported at baseline and 3 months postpartum. ***Social Adjustment*** will be assessed using the 14‑item screener version of the Social Adjustment Scale – Self-report (SAS‑SR) (91, 92). Six major areas are covered: work (paid or unpaid), social and leisure activities, relationships with extended family, role as marital partner, role as a parent, and role within the family unit (including perceptions about economic functioning). For this study, we will only use the work subscale at 3 months postpartum. ***Marital satisfaction*** will be evaluated with the short version of the Dyadic Adjustment Scale (DAS-7) (93-95) at 3 months postpartum. ***Co-parenting.*** The proposed intervention is partner-inclusive and, as such, may improve co-parenting quality (the extent to which parents work together and agree on childcare and education). We will use a brief 14-item version of the Coparenting Relationship Scale (75) (e.g., partner pays a great deal of attention to our child; partner appreciates how hard I work at being a good parent) at 3 months postpartum. ***Social Support*** will be assessed at 6 months postpartum using the 10-item Social Provisions Scale (SPS-10) on emotional

support or attachment, social integration, reassurance of worth, tangible help, orientation, and opportunity for nurturance (96, 97).

Parent and child assessments. Maternal depression has repeatedly been associated with poorer quality mother-infant relationships, attachment, and child-emotional development. ***Parenting*** will be assessed at 6 months postpartum with the Parent's Cognition and Conduct Toward the Infant Scale (ÉCOPAN) (98). ***Child social, emotional and cognitive development.*** The Ages and Stages Questionnaire 3rd edition (ASQ-3) is a widely used parent-reported scale covering physical, social, emotional, and cognitive child development at ages one month to 5 ½ years. Its parent-centric approach and inherent ease of use have made it the most widely used developmental screener in the world (99). ***Child difficult temper*** will be evaluated at 6 months postpartum with the Infant Characteristics Questionnaire (ICQ) (100, 101).

Other variables (effect modifiers). ***Compliance to the intervention***. Participant and partner use will be calculated automatically using web-based statistics and the number of modules completed will be self-reported.The number of calls with the nurses will also be recorded. ***Intervention Team Activity Log.*** All intervention activities (telephone discussions, voice messages, missed sessions) will be documented. ***Personality disorders symptoms.*** These may be important modifiers of the intervention and thereby impact compliance. We will use the 25-item Personality Inventory for DSM-5 Brief Form (PID-5 BF) (102). Groups will be created using a 30% cut-off score for each subscale. ***Gender roles.*** Using data at T_2 we will create a gender role score for participants and partners by identifying gender-related variables such as employment status, income; gender roles assessed using the Bem Sex Role Inventory (BSRI) (103, 104). Sex of the child will also be tested as a potential effect modifier. ***The sociodemographic and medical history.*** Information will be collected about the household, employment status, revenue, education level, ethnicity, reproductive history, COVID-19 infection history and weight.

Economic evaluation. Service utilization will be measured using a slightly modified version of the ***Health Service Utilization and Cost of Care Questionnaire*** (105) to assess childcare expenses and travel costs incurred by patients to obtain care. Costs of administering the intervention include a) recruiting and training of nurses, b) nurses' time to provide the intervention, and c) supervision of nurses.

Planned Analyses

Data will be analyzed using SAS software using an intent-to-treat approach. A two-sided significance level of 0.05 will be used for the primary outcome; a significance level of 0.01 (two-sided) will be used for secondary and other outcomes to account for multiple outcomes. Demographic and other baseline variables will be compared between study groups using descriptive statistics (mean, standard deviation, proportions).

For the primary outcome, a two-sample sided test of proportion (chi-square test) will be used to compare the difference in the proportion of women with EPDS in the clinical range (> 13) at 3 months' postpartum. The same approach will be used for the 6-month assessment (secondary outcome). These analyses will be supplemented by an analysis using EPDS scores, where the baseline EPDS score will be used as covariate in an ANCOVA model including the 3- and 6-month EPDS scores. With this model, we will obtain 95% confidence intervals of EPDS score differences between intervention arms at 3 and 6 months' postpartum. Sensitivity analyses will be performed to investigate the potential bias introduced

by attrition. A method based on inverse-probability-of-attrition weights (IPAWs) will be used (101, 102).

For secondary outcomes, the statistical method for comparing intervention arms will depend on the distribution of the outcome variable. For binary variables, chi-square tests will be used. The corresponding 95% CI for the difference in proportions will also be provided. In the unlikely event that randomized intervention arms are unbalanced for baseline variables known to be associated with primary and secondary outcomes, logistic regression will be used where unbalanced variables will be included. For continuous variables, we will use ANCOVA models as described above. Again, unbalanced variables will be added if needed. If the intervention is found to be effective, exploratory analyses will be conducted to explore the potential effect of moderator variables using causal inference models including gender and intervention compliance (103, 104). No formal interim efficacy analysis is planned. Ethical practices and conduct of the trial as well as all safety concerns will be reported to an independent Data and Safety Monitoring Committee.

Planned subgroup analyses. The ANCOVA models presented above will be expanded to include the socioeconomic status of the participant, ethnicity, personality disorder symptoms subgroup variable as well as interaction with the intervention.

Pilot Study

We conducted a feasibility study to assess acceptability and compliance to the intervention (n = 17). Pilot data indicate that women used a mix of electronic devices to access the intervention. All used an iPad at some time, 40% also used their smartphone and 20% also used a computer. Telephone follow-up by a nurse was rated as “essential” (40%), “very useful” (40%), or “useful” (20%). Online sessions were rated as “very useful” (60%) or “useful” (40%). Strategies proposed in the intervention (cognitive restructuring, relaxation, behavioral modification, social support) were used “regularly” (30%), “often” (50%), “occasionally” (10%), or “never” (10%). The material was rated as “very easy to understand” (90%) or “easy” (10%). Each strategy was used at least occasionally by 86% of women. Qualitative data indicated high levels of appreciation (Appendix A).

Ethical considerations

Voluntary informed consent

The recruiting process will allow women to give a voluntary informed consent (Appendix E). The consent form will be signed on the online platform provided by the URCA.

Confidentiality and Privacy Protection

The trial manager will obtain signed confidentiality agreements from research assistants. All baseline and outcome data will be collected via online questionnaires using REDCap and stored in an anonymized database on a secure server at URCA. Data will remain strictly confidential and will not be disclosed to members of our intervention team or the partner. Data safety will be maximized through electronically protecting access to computers and servers, use of fire walls. Coding standards will be developed by the executive committee and communicated to the Data Management Committee (DMC) who will ensure that confidentiality of data is ensured. The intervention coordinator and trial manager will

also report to the DMC any adverse events arising from the interventions, including situations in which additional interventions were required following disclosure of risk by a participant or during an assessment or intervention session. Independent Data and Safety Monitoring Committee (DSMC) will consist of experts not involved in the planning and conduct of this study, with no conflicts of interest or obligations to the investigator. A database of adverse events will be maintained by the DMC and annual reports will be sent to the Data and Safety Management Committee (DSMC). At the end of the study, data will be transferred on the University of Montreal's server (UNIX) (see Appendix O for bank protocol).

Exercises responses stored on the website will be secured. None of the answers given by participants will be analyzed as part of the study. These exercises are exclusively an educational tool from the intervention. Professionals and partners will not have access to this content.

The Parents and Babies program is a research project and is not part of the usual services provided. Personal outcomes from the intervention will not have any clinical impact that would require follow-up from the medical team. For this reason, participation will not be indicated in the participants' medical record. This intervention is validated in other populations (American pregnant women in the general population) and formats (in person 1:1 or group session, fully automated web-based course).

Risks to Participants

Counseling interventions received a grade B recommendation from the USPSTF (2), reflecting the low level of risk and high probability of a moderate net benefit. None of the included studies, however, offered virtual counseling and there is very little evidence of the efficacy of virtual prevention interventions. As in all studies where participants report on their mental health, there is always the possibility that participants become more aware of their symptoms. We will minimize risk to participants by taking the following measures. First, at the end of each assessment, there will be a list of resources to manage mental health issues (Appendix M). The list will include contact information for: 1) in Quebec, Integrated University Health and Social Services Centres (CIUSS). These local community health centers offer prenatal classes, telephone call services, and links to psychosocial and mental health services; 2) family physician clinics; 3) obstetric clinics, and; 4) emergency phone numbers and help lines. Second, we will set up a telephone line to answer questions about the study and remind participants of available resources. Third, participants with a positive response on the EPDS self-harm ideation item or scoring above the clinical EPDS cut-off ($\geq$ 13) during screening or follow-up will be notified by a pop-up at the end of the questionnaire. The pop-up will inform them they will receive a phone call from a nurse of our team and encourage them to speak to their doctor and contact resource links (Appendix N). The nurse will make the call within 24 hours to evaluate the suicidal risk and make sure the participant is taken in charge by appropriate health services.

Expected Results and Benefits

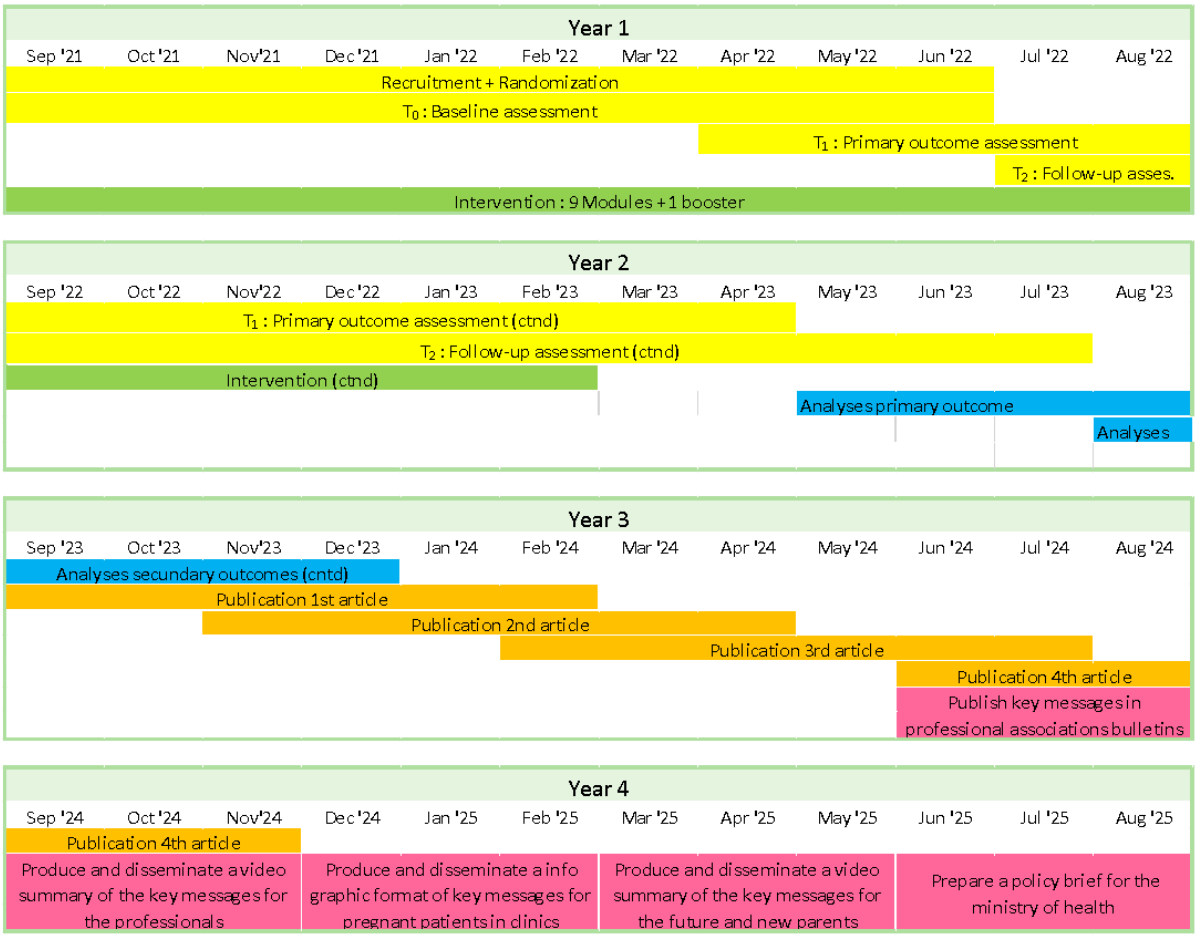
This project will 1) provide virtual support related to the program content to women with symptoms of depression (moderate severity) in a context where individual medical and psychosocial follow-ups are minimized due to the pandemic; 2) prevent the worsening of depression and anxiety, improve stress management, and potentially improve obstetric outcomes and prevent child development disorders associated with maternal disorders; 3) develop an online economic intervention for pregnant women in situations of social isolation or activity limitations due to various causes (e.g., pandemic, strict rest at home); 4) facilitate the coordination of virtual social support by maternal and child physical health specialists and

mental health specialists; 5) test a low-cost intervention with the potential to reduce third-line mental health care costs and thus increase effectiveness in regular practice, and; 6) to promote the evolution of interdisciplinary perinatal practices and to deepen the integration of perinatal mental health practices into the Mother-child program at Sainte-Justine University Hospital.

Timeline

We plan to complete activities in 4 years, with 2 years allocated to intervention and follow-up. Figure 4 presents details of the study timeline.

Figure 4. Study timeline


Year 1
Sep '21
Oct '21
Nov'21
Dec '21
Jan '22
Feb '22
Mar '22
Apr '22
May '22
Jun '22
Jul '22
Aug '22
Recruitment + Randomization
T0 : Baseline assessment
T1 : Primary outcome assessment
T2 : Follow-up asses.
Intervention : 9 Modules +1 booster
Year 2
Sep '22
Oct '22
Nov'22
Dec '22
Jan '23
Feb '23
Mar '23
Apr '23
May '23
Jun '23
Jul '23
Aug '23
T1 : Primary outcome assessment (ctnd)
T2 : Follow-up assessment (ctnd)
Intervention (ctnd)
Analyses primary outcome
Analyses
Year 3
Sep '23
Oct '23
Nov'23
Dec '23
Jan '24
Feb '24
Mar '24
Apr '24
May '24
Jun '24
Jul '24
Aug '24
Analyses secundary outcomes (cntd)
Publication 1st article
Publication 2nd article
Publication 3rd article
Publication 4th article
Publish key messages in professional associations bulletins
Year 4
Sep '24
Oct '24
Nov'24
Dec '24
Jan '25
Feb '25
Mar '25
Apr '25
May '25
Jun '25
Jul '25
Aug '25
Publication 4th article
Produce and disseminate a video summary of the key messages for the professionals
Produce and disseminate a info graphic format of key messages for pregnant patients in clinics
Produce and disseminate a video summary of the key messages for the future and new parents
Prepare a policy brief for the ministry of health

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