Group CBT for Perinatal Anxiety: A Randomized Controlled Trial

Study Protocol and Analysis Plan

July 16, 2021

NCT04581681

PROTOCOL

Research Problem/Background Analyses/Relevant Literature:

Research focus on mental health during the perinatal period, defined as ranging from the beginning of pregnancy to 12 months postpartum (O'Hara & Wisner, 2014), has to date largely been on identification and treatment of perinatal depression (Gavin et al., 2005). Increasingly, it is being recognized that symptoms of anxiety, not just depression, occur during the perinatal period and are debilitating (Goodman, et al., 2016). Research suggests that the prevalence of anxiety disorders is actually higher than that of depressive disorders (11.1% versus 6.1%; Wenzel et al., 2005).

Anxiety during pregnancy has been associated with negative consequences for fetal and infant development (Beijers, Jansen, Riksen-Walraven, & de Weerth, 2010). Anxiety during pregnancy is also associated with an increased rate of C-section deliveries, reduced duration of breast-feeding, and increased utilization of health care services by the mother (Paul, Downs, Schaefer, Beiler, & Weisman, 2013). Further, anxiety during pregnancy may have an adverse effect on the mother-child relationship (Goodman et al., 2016). Anxiety during pregnancy is also a risk factor for the development of postpartum depression (PPD; Farr et al., 2014; Rambelli et al., 2009; Sylven, Thomopoulos, Kollia, Jonsson, & Skalkidou, 2017). The additional negative effects of PPD are well documented (e.g., Field, 2010).

It is easy to understand why the perinatal period is a vulnerable time with respect to the onset and/or exacerbation of anxiety symptoms. Shifting hormones may affect and or initiate symptoms of physical anxiety and/or panic attacks, particularly as increased estrogen and progesterone may stimulate respiration and lead to hyperventilation (Karsnitz & Ward, 2011). Physical symptoms of pregnancy may also trigger anxiety as the mother may interpret benign symptoms as a sign that there is something wrong with the fetus. Further, the pregnancy and postpartum period are times of significant life change and stress (Geller, 2004), a risk factor for the development of an anxiety disorder (Khan & Khan, 2017). Childbirth, in particular, is experienced by many women as stressful and, indeed, up to one-third of women perceive their experience of childbirth as traumatic (e.g., Soet, Brack, & Diiorio, 2003). High stress during childbirth raises risk for negative maternal outcomes, including the onset of anxiety disorders (Bailham & Joseph, 2003; Dekel, Stuebe, & Dishy, 2017).

There is substantial interest in non-pharmacological interventions for the perinatal phase given the concerns about side-effect profiles of psychotropic medications and potential impact on the developing fetus or breastfeeding infant (Ride & Lancsar, 2016). Cognitive behavioural therapy (CBT) is well established as an evidence-based treatment approach for anxiety disorders (see Norton & Price, 2007, for a review). Perinatal anxiety may have a specific focus on themes related more directly to pregnancy, labour and delivery, and postpartum issues. These may include health and wellness of baby and concerns about parenting skills (Jacob & Storch, 2013). It is therefore important that psychological treatment targets both general anxiety symptoms, and specific perinatal anxiety symptoms, in order to lead to greater wellness and reduced negative impact on the mother, fetus, and baby.

To date, there have been only a few studies evaluating treatments with this population due to historic lack of awareness in the healthcare profession about the extent and impact of this problem (Goodman et al., 2016). There is one randomized controlled trial (RCT) demonstrating that intensive individual CBT was effective for postpartum OCD (Challacombe, Salkovskis, Woolgar & Wilkinson, 2017). This intervention was superior to treatment as usual, and had a low drop-out rate (Challacombe et al., 2017). More recently, Green et al. (2015) described positive outcomes with a pilot study (n = 10) of a 6- session CBT group. The treatment exhibited significant reductions in anxiety and depression and was highly acceptable to patients (Green et al., 2015). Their intervention modified CBT for the perinatal population by including perinatal examples in their protocol and by including CBT for depression elements, given the high comorbidity of depressive symptoms often seen in this population (Green et al., 2015). Thus, although the scant literature is promising, sample sizes have been small and there has been no RCT examining the effectiveness of CBT for perinatal anxiety disorders. Further, to the best of our knowledge, the current interventions have not explicitly included an additional focus on issues relevant to this population. These include explicit discussions on strengthening bond with baby, valuing self-care, learning how to ask others for help, and tackling myths about motherhood (e.g., being a "supermom", that you should love every minute with your child), among other pertinent topics (see Design and Methodology for treatment description).

Our clinic has developed a group CBT protocol for perinatal anxiety disorders (Furer, Alcolado, Reynolds, & Hebert, *in preparation*). Results from a pilot study were significant with large effect sizes. Examining changes in anxiety revealed significant reductions from pre- to post-treatment on the *Perinatal Anxiety Screening Scale* (Somerville et al., 2014), $F(1,28) = 53.36$, $p < .001$, *partial η2* = .66. Significant reductions in depression were also seen from pre- to post-treatment, as measured by the *Edinburgh Postnatal Depression Scale* (Cox, Holden, & Sagovsky, 1987), $F(1,29) = 28.83$, $p < .001$, *partial η2* = .50. **The primary aim of the proposed study is to evaluate the effectiveness of group cognitive-behavioural therapy for perinatal anxiety in a randomized controlled trial**. We will randomize to the treatment group and to the waitlist control group and conduct 1-month and 3-month follow-up assessments, to determine the effectiveness and acceptability of the intervention. Based on the promising pilot results, we expect to be successful in our endeavor. This will be the first RCT of group CBT for perinatal anxiety, contributing substantially to the literature supporting this intervention for this large and vulnerable population. When disseminated, it will have the potential to positively impact health and mental health outcomes for mothers, fetuses, and children.

Study Objectives:

Our large-scale objectives are to determine the effectiveness of the treatment, by replicating our pilot study results and comparing the group CBT-PA to a waitlist control group for the first time. We also want to examine the acceptability of treatment in group format for this population. Therefore, the specific objectives are as follows:

1) Replication and extension of previous pilot study findings. Our pilot study (N = 40) found a significant reduction in symptoms of both anxiety and depression from pre to post CBT-PA. The next step is to replicate and extend these findings in a randomized controlled trial (RCT).

2) Compare the effectiveness of the treatment to control treatment: The pilot study determined the feasibility and acceptability of group CBT-PA. The goal of the current study is to evaluate effectiveness of CBT-PA by conducting an RCT that will include a treatment condition and a waitlist control condition.

3) Determine the long-term durability of the treatment effects: A secondary goal is to evaluate durability of treatment gains with group CBT-PA. 1-month and 3-month follow-up assessments will therefore be administered.

4) Confirm the relevance and acceptability of this treatment to the perinatal population. It is important to consider patient preferences and as such we are administering a standardized questionnaire as well as a general patient satisfaction questionnaire to verify that participants have positive impressions of the treatment.

5) To examine whether the degree of childbirth stress moderates patient response to the intervention CBT for perinatal anxiety. This will inform future refinements of the treatment.

6) Determine whether CBT for perinatal anxiety improves maternal efficacy and attachment.

Hypotheses:

1. Perinatal anxiety group treatment will be effective in reducing symptoms of perinatal anxiety
2. Perinatal anxiety group treatment will be superior to the waitlist control condition at reducing symptoms of perinatal anxiety
3. Reduction of perinatal anxiety symptoms (treatment gains) will be maintained at 1-month and 3-month follow-up
4. Perinatal anxiety group treatment will be rated as acceptable to the perinatal anxiety population
5. Women with severe levels of childbirth stress will show poorer postpartum adjustment (i.e., higher PASS and EPDS scores) pre-treatment compared to women with non-severe levels of childbirth stress
6. Birth stress and treatment will interact to predict postpartum adjustment. Specifically, following treatment there will be no significant differences in postpartum adjustment between women in the CBT group with severe versus non-severe childbirth stress. However, there will continue to be a significant difference in postpartum adjustment between women with severe versus non-severe childbirth stress in the control condition.
7. CBT for perinatal anxiety will improve maternal efficacy and attachment, and this will be predicted by degree of anxiety symptom improvement.

Design and Methodology:

Participants:

We will recruit 58 women with perinatal anxiety (defined as ranging from the beginning of pregnancy to 12 months postpartum; O'Hara & Wisner, 2014). Approximately 29 participants will be randomly assigned to the treatment condition (CBT-PA) and 29 participants will be randomly assigned to the waitlist control (WC) condition. This sample size is adequately powered for the statistical analyses (see Statistical Plan, below), and includes an initial sample size of 50 with an extra 8 participants included based on predicted 15% attrition rate from the pilot study.

Participants will be recruited in three ways: (1) Perinatal patients referred to the Anxiety Disorders Clinic (ADC) at St. Boniface Hospital (through a participant letter of invitation or flyer), (2) community perinatal individuals self-referred or referred by healthcare professional to the Psychological Service Centre (PSC), the Clinical Psychology training clinic located in the Psychology Department at the University of Manitoba (through a participant letter of invitation) and (3) advertisements in the newspaper, as well as at the department of Obstetrics, Gynecology, and Reproductive Sciences at the University of Manitoba, local community and health organizations. These organizations include the Anxiety Disorders Association of Manitoba, the Birth Centre, Women's Health Clinic, and Nest Family Centre. Obtaining the desired sample size of 58 from these venues is reasonable given the number of perinatal anxiety referrals the ADC alone typically receives in a year is now approximately 200. In conjunction with the active recruitment we will do through the PSC and with the additional advertisement, we should easily meet our target. If needed, we also have a budget to place our advertisement in the newspaper three times throughout the year.

Women will be eligible for participation if they are pregnant or within 12-months postpartum. Additional inclusion criteria are that participants are 18 or older and meet criteria for at least one anxiety or related disorder (i.e., generalized anxiety disorder, social anxiety disorder, panic disorder with or without agoraphobia, obsessive-compulsive disorder, or posttraumatic stress disorder). Exclusion criteria will include primary perinatal depression, active suicidality and/or homicidality, active psychosis, mania, or a substance use disorder that would interfere with participation in the treatment. Additionally, women must not be receiving concurrent psychotherapy and if on medication, must not have made any medication changes in the 6 weeks prior to beginning participation our study. These inclusion and exclusion criteria will be assessed during the diagnostic interview process (see Procedure, below). Please note that although participants are asked whether they give consent for their family physicians to be aware of the treatment they are receiving, refusal to give consent to do so will not be considered an exclusion criterion.

Materials:

Interviews:

The *Mini International Neuropsychiatric Interview* (MINI; Sheehan et al., 1998) Version 7.0.2 will be administered at the initial assessment appointment to diagnose presence of an anxiety disorder and any other co-morbid conditions according to the to the Diagnostic and Statistical Manual of

Mental Disorders, 5th Edition (DSM-5; American Psychiatric Association, 2013). The MINI takes approximately 1 hour to administer.

The *Hamilton Anxiety Rating Scale* (HAM-A; Hamilton, 1959) is a 14-item clinician-administered interview scale used to assess the severity of anxiety symptoms. It is widely used in clinical research trials (Thompson, 2015) will be used in the present study to examine changes in anxiety symptoms from pre- to post-treatment. This scale has acceptable reliability and concurrent validity (Maier et al., 1988) and takes approximately 10-15 minutes to administer (Hamilton, 1959). The HAM-A will be administered at the assessment visits.

Birth Experience Interview (BEI; Harkness et al., 2008): Stress of the birth will be assessed using the BEI, a semi-structured investigator-based contextual interview. Women will be asked a series of specific questions about their childbirth experience (e.g., Did you have a C-section?), followed by probing questions to elicit contextual information (e.g., Was the C-section planned?). Interviews will be conducted either at the assessment visit following the MINI interview or over the telephone at the convenience of the participant. The interview will be audio-recorded and subsequently rated according to a coding manual. The BEI interview takes approximately 30 minutes to administer.

Qualitative Interview Protocol and Questions. At the post-treatment visit, individual, semi-structured qualitative interviews will be completed with approximately 15 participants in the active treatment group and 15 participants in the waitlist control condition. These questions were developed by our research time. For participants in the active treatment group, the objectives of the qualitative interview are to better understand participant experiences in the intervention; hear from participants about their perceptions of the specific components of the intervention and the impact of those components; learn about the barriers to participating in the intervention; and ways of improving the intervention. For participants in the waitlist control group, the qualitative interview is aimed at understanding the experiences of the waitlist participants. Specifically, how they have experienced being on the waitlist; current perceptions of their distress and mental/emotional functioning; what resources or services were accessed during their waitlist enrollment; the impact of those resources and/or services on their distress and mental/emotional functioning; and their anticipatory thoughts regarding participation in the Overcoming Anxiety During Pregnancy and Postpartum Intervention. Probes will be used throughout the interviews to gather richer information. will be audio-recorded and transcribed using transcription software. Interviews will be analyzed according to thematic analysis (Braun & Clarke, 2006).

*The Coronavirus Stress Survey (*McLean & Cloitre, 2020) is a 10-item survey that was developed for to evaluate the impact of the coronavirus pandemic on patient lives. We are using it in the current study such that if necessary we can go back and examine the impact that the coronavirus had on different participants depending on at what point in the pandemic they participated in the study, in case it could be differentially impacting study results.

Questionnaires:

Demographic Questionnaire. At the initial assessment participants will complete a demographic data form. This will include information on age, perinatal status (i.e., pregnant or postpartum), stage of

pregnancy if pregnant, age of infant if postpartum, number of pregnancies, number of children, level of education, family income, ethnicity, marital status, medication status, prior mental health diagnoses and prior help-seeking. Additional information on difficulties with conception, pregnancy, miscarriages, labour and delivery, and mother and baby health postpartum will be collected to help characterize our sample.

The *Edinburgh Postnatal Depression Scale (Cox, Holden, & Sagovsky, 1987; EPDS)* is a 10-item self-report measure assessing symptoms of postnatal depression on a 0 to 4 scale. It exhibits satisfactory psychometric properties, is sensitive to change (Cox et al., 1987), and has excellent test-retest reliability (Kernot, Olds, Lewis, & Maher, 2015). It is also considered acceptable for use in pregnant populations (Murray & Cox, 1990). It will be used in the present study to examine changes in depression symptoms across treatment. The EPDS will be administered at the intake assessment, post-treatment assessment, 1- and 3-month follow-up assessments, and weekly during treatment.

The *Experiences in Close Relationships – Revised Questionnaire (Fraley, Brennan & Waller, 2000; ECR-R).* The ECR-R is a 36-item self-report measure that assesses adult attachment style. The ECR-R will be administered at the initial intake assessment.

The *Group Climate Questionnaire (GCQ; Mackenzie, 1983).* The GCQ is a 12-item self-report measure that assesses individual group member's perceptions of the group's therapeutic environment. The GCQ will be administered during treatment sessions at weeks 2, 4, and 6.

Maternal Antenatal Attachment Scale (MAAS; Condon, 1993). The MAAS is a 15-item self-report measure that assesses maternal attachment towards her unborn baby in the antenatal period. This measure will be administered to women who are participating in the study during the prenatal period. The MAAS will be administered at the intake assessment, post-treatment assessment, and at the 1- and 3month follow-up assessments to pregnant women.

Maternal Efficacy Questionnaire (MEQ; Teti & Gelfand, 1991): The MEQ is a 10-item self-report measure that assesses a mother's perception of her own parenting competence. The MEQ will be administered at the intake assessment, post-treatment assessment, and at the 1- and 3month follow-up assessments.

Maternal Postnatal Attachment Scale (MPAS; Condon & Corkindale, 1998). The MPAS is a 19-tem self-report measure that assesses maternal attachment towards her infant during the postnatal period. This measure will be administered to women who are participating in the study during the postpartum period. The MPAS will be administered at the intake assessment, post-treatment assessment, and at the 1- and 3-month follow-up assessments to postpartum women.

Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983): The PSS is a 10-item self-report measure that assesses the extent to which one's life is appraised as stressful. The PSS will be administered at the intake assessment, post-treatment assessment, 1- and 3-month follow-up assessments, and weekly during treatment.

The *Perinatal Anxiety Screening Scale* (Somerville et al., 2014; PASS) is a 31-item self-report measure assessing symptoms of anxiety during the perinatal period. It will be used in the current investigation to examine changes in anxiety symptoms across time. The scale has excellent reliability, adequate test-retest reliability, and strong evidence of convergent validity (Somerville et al., 2014). The PASS will be administered at the intake assessment, post-treatment assessment, 1- and 3-month follow-up assessments, and weekly during treatment.

Post-Delivery Perceived Stress Inventory (PPSI; Razurel et al., 2014): The PPSI is a 29 item self-report measure of the degree of stress experienced as a result of the birth experience specifically. The PPSI will be administered at the intake assessment to postpartum women.

The *Treatment Acceptability/Adherence Scale* (Milosevic, Levy, Alcolado, & Radomsky, 2015; TAAS) is a self-report measure of treatment acceptability which exhibits sound psychometric properties. It will be administered at treatment outset to determine the perceived acceptability of the treatment to participants.

The *Treatment Satisfaction Measure (TSM)* was developed for use in our clinic to evaluate patient impressions of treatment. Four items regarding the helpfulness of the sessions, the group aspect, the workbook, and the focus on perinatal issues are rated on a 5-point scale (i.e., from "very helpful" to "not at all helpful"). Two additional yes/no questions are included, regarding whether participants would recommend the program to other perinatal women and whether they themselves would participate in the group again if needed. Two final open-ended questions are included regarding what patients liked about group, and any suggestions they would have for changes to future groups. It will be administered at the post-treatment assessment.

The Homework Checklist is a list of all the homework assignments from each session (e.g., read the chapter in the workbook, worked on relaxed breathing, exposure, coping statements, etc.). Participants will complete it out at each session regarding the previous weeks' homework assignments, whether they worked on each element, for how long, and any comments they might have.

The Treatment Protocol Adherence Checklist is a checklist copy of the group leader's guide to each session, with a spot to check off if each element was covered, and open-ended questions regarding deviations from the protocol and other session occurrences of note. Group leaders will complete this checklist at the end of each group session.

Intervention:

The group CBT intervention for perinatal anxiety has been formalized with session guides for the facilitators and a workbook, "Overcoming Anxiety in Pregnancy and Postpartum" (Furer & Reynolds, 2015), developed by members of our Anxiety Disorders Clinic. There are 6 core modules covered over the 6 treatment sessions, including: (1) Understanding anxiety during pregnancy and postpartum, (2) self-care, (3) setting goals and facing fears, (4) nurturing the developing relationship with baby, (5) coping with negative thoughts and worries, and (6) relapse prevention. Content is based on general principles of CBT for anxiety but specific themes and examples are geared towards

the pregnancy and postpartum periods. For example, instead of general worries, worries regarding baby are covered. Instead of social anxiety regarding one's performance, examples about avoiding situations in case others will judge parenting or baby crying are explored. Distorted cognitions are also explored, with an additional focus on beliefs about motherhood and perfectionism.

Procedures:

Recruitment: Participants recruited through the ADC or the PSC will be invited to participate in the research study at time of referral through a note on the letter they receive from our respective clinics acknowledging that we have received their referral. Additionally, clinicians may show study posters to potential participants at the time of their standard clinic intake appointment. Interested participants will be directed to use the study contact on the poster to get more information and/or provide their contact information for the clinician to pass on to the research assistant so they can be contacted to receive further information. This will be particularly helpful the beginning of the study, where participants who have already been on our waiting list for several months will not have received the letter of invitation regarding the study with their letter from the clinic acknowledging receipt of their referral. They will be assured that their decision to participate in research will in no way affect their ability to take part in clinical services. Women who decline to participate in the research study will still take part in the standard clinic intake process and will be given the opportunity to attend our regular perinatal anxiety groups.

Women recruited via response to community advertisements will be invited to the research assessment visit.

Initial Assessment: At the research assessment visit all participants will undergo the informed consent process (form will be signed electronically via Survey Gizmo), and be administered the MINI by a trained research assistant to formalize and standardize diagnostic status. These assessments will be audio-recorded for reliability coding. An independent rater will review a random selection of 10% of the assessments to determine the degree of agreement on diagnoses. Participants will also complete the BEI at the time of assessment, which will also be audio-recorded for scoring purposes. The interviews will be conducted either via videoconference (either Zoom Professional or Microsoft Teams) t. Lastly, at this visit participants will also complete the demographic questionnaire, as well as PPSI, MAAS or MPAS (depending on whether the woman is pregnant or postpartum), MEQ, PSS, PASS, ECR-R, and EPDS measures. These questionnaires will be completed online via SurveyGizmo, a secure survey platform.

Random Assignment: We will be using block assignment as we are delivering group intervention and not individual intervention. This means that after the first 6-8 eligible participants have entered the study, their "block" will be randomly assigned to participate in the CBT-PA or WC condition. The next 6-8 participants will be randomly assigned again, and so on, until we reach our target sample size.

Participants CBT-PA condition will receive the treatment immediately. In the WC condition they will wait 10 weeks for the intervention (see Procedural Timeline below). This 10-week time frame includes the 6 weeks during which participants in the CBT-PA condition receive the treatment, as

well as the 1-month follow-up period. Please note this 10-week waiting period is still less time than our currently clinical wait-time for this service, which is between 16-20 weeks.

Treatment: The group intervention will consist of 6 treatment sessions that are 1.5 hours each. Participants are invited to bring their infants to sessions as needed, in order to reduce barriers to attending. Participants will take part in groups virtually, via videoconferencing platform, Zoom Professional coordinated through ADC or the PSC, depending on preference and timing of groups (as part of our regular clinical service we typically advertise potential group times across the two clinics to help maximize patient ability to attend a group that works for their schedule). These sessions will be co-facilitated by a clinical psychologist and a trainee (i.e. research assistant, staff member, or Clinical health Psychology resident). Group size will typically range from 6-8 members. With a sample size of 29 in the CBT-PA condition, this means we will likely run 4-5 groups for the CBT-PA condition and 4-5 additional groups for those in the WC. During the treatment phase for all participants, the TAAS will be administered at the beginning of the second session to gauge first impressions of treatment. The TSM will be administered at the final treatment session to elicit participant feedback regarding treatment. The PASS, PSS and the EPDS will be administered weekly during treatment. The GCQ will be administsered at weeks 2, 4, and 6 of group. These questionnaires will be completed online via SurveyGizmo, a secure survey platform. Additionally, the group leaders will complete the integrity checklist at the end of each treatment session to assess the degree to which session protocol was adhered to, also via SurveyGizmo.

Subsequent assessments:

The CBT-PA participants will complete the same questionnaire battery as at the initial assessment again post-treatment, again at 1-month post-treatment, and at 3-months post-treatment. The assessments will occur virtually, via videoconferencing platform. The questionnaires will be completed online via SurveyGizmo, a secure survey platform. They will also be administered the HAM-A by study clinicians at these time points, via Microsoft Teams or Zoom.

The WC participants will complete the questionnaire battery after waiting 6 weeks (to be a comparison to the post-treatment assessment for the CBT-PA group) and again after waiting 4 more weeks (to be a comparison to the CPT-PA group for their 1-month post-treatment assessment). Then the WC participants will receive the treatment (including assessment measures that occur during the active treatment) and complete a final post-treatment assessment (see graphic below depicting progress through the assessment and treatment visits). These questionnaires will be completed online via SurveyGizmo, a secure survey platform.

Qualitative Interviews:

Individual, semi-structured qualitative interviews will be completed with approximately 15 participants in the active treatment condition (sample A), as well as 15 participants in the control condition (sample B). These interviews will be completed via Microsoft Teams or Zoom Professional and will be audio-recorded. These will take place during X time.

Debrief: Following the completion of final assessment visits, patients will be fully debriefed as to the full purposes of the study.

Compensation:

Participants will be offered $10 at the end of each assessment visit (for a maximum of $40 per participant), as a monetary compensation for participants time and efforts, as well as to offset the costs of transportation for their appointments. They will not be offered compensation for their treatment visits.

Timeline:

Dates	Tasks
April 2020	• Funds released • Recruit, hire, and train paid personnel • Assemble study materials • Begin recruitment of participants • Begin intake assessments
May – July 2020	• Begin running treatment groups • Data entry
July – December 2020	• Begin conducting 1 & 3-month follow-up appointments • Continue with recruitment • Continue with treatment groups • Continue with data entry
January – March 2021	• Analyze data • Prepare press release • Prepare knowledge translation talk • Apply to academic conferences • Draft manuscript

Procedural Timeline:

Condition	**Initial Assess**	**Tx for Active group**	**Post-Assess for CBT-PA/2nd Assess for WC**	**1-Month Follow-Up for CBT-PA/3rd Assess for WC**	**Tx for WC**	**Post-Assess for WC**	**3-Month Follow-Up for CBT-PA**
CBT-PA Group	✓	✓	✓	✓	×	×	✓
WC Group	✓	×	✓	✓	✓	✓	×

Tx = Treatment
Assess = Assessment
✓ = Study visit at this time point

× = No study visit at this time point

Statistical Plan:

This is a randomized controlled trial with a waitlist control. Intent-to-treat (ITT) analyses will be conducted in order to accurately depict the progression of all participants through this treatment. As such, if there is drop-out, the last observation point for those participants will be carried forward for all subsequent missing data points of interest. **To test hypotheses 1 and 2** (1 - that the treatment be effective, and 2 – as compared to the control group), two mixed-model ANOVA will be conducted. The between-participants' independent variable will be treatment condition (CBT-PA vs. WC), and the within-participants' independent variable will be time point (pre-treatment, post-treatment). The dependent variables will be the PASS and the EPDS. Power analyses conducted using G*power (Faul, Erdfelder, Lang, & Buchner, 2007) indicated the sample size of 50 participants (25 in each condition) will provide more than adequate power for all analyses, therefore the total sample size of 58 participants includes an additional 8 participants to account for a predicted 15% attrition rate. For the ANOVA, assuming a large effect size (based on the large effect size of our pilot study findings), 2 conditions, 2 time points, and requiring a high level of power, a minimum total sample size of 40 is needed. **To test hypothesis 3** (that treatment effects will be durable over time), two repeated measures ANOVA will be conducted on the CBT-PA group. The within-subjects' independent variable will be time point (post-treatment to 1-month follow-up) and the dependent variables will be the PASS and the EPDS. Power analyses conducted using G*power (Faul, Erdfelder, Lang, & Buchner, 2007) indicate the proposed sample size of 25 participants will provide more than adequate power. For this ANOVA, assuming a large effect size, 2 time points, and requiring a high level of power, a minimum total sample size of 15 is needed. Analyses will then be re-run just examining the CBT-PA group and their changes from post-treatment to 3-month follow-up. **To test hypothesis 4** (that treatment will be acceptable to participants), descriptive analyses will be conducted to examine the mean scores on the TAAS to determine the treatment's acceptability. Further examination of the ratings of the components of treatment (e.g., workbook, group format), and summary of themes from the open-ended questions will help determine specifically what participants liked and did not like about the treatment. **To test hypotheses 5 and 6** (that childbirth stress moderates treatment outcome), we will conduct mixed-effects random regression models. Post-treatment scores (i.e., PASS and EPDS) will be entered as the DV in separate analyses. Baseline scores, treatment group (CBT-PA verses WC), childbirth stress score, and the interaction term (treatment group x childbirth stress score) will be entered as predictors. Significant interactions will be followed up at the level of childbirth stress. We found significant effects of childbirth stress on treatment response in a previous study with a sample size of 52 (Shamblaw et al. submitted). **To test hypothesis 7** (that CBT-PA improves maternal efficacy and attachment), we will conduct two mixed-model ANOVAs. The between-participants' independent variable will be treatment condition (CBT-PA vs. WC), and the within-participants' independent variable will be time point (pre-treatment, post-treatment). The dependent variables will be the MPAS/MAAS and the MEQ. These results will help inform future modifications to the protocol, for the benefit of all patients. Power analyses conducted using G*power (Faul, Erdfelder, Lang, & Buchner, 2007) indicated the sample size of 50 participants (25 in each condition) will provide more than adequate power for this analysis.

Audio-recorded qualitative interviews will be transcribed using transcription software and will be analyzed according to thematic analysis (Braun & Clarke, 2006).

Budget Details and Available Resources:

Contract with Funder:
This study is supported by a Manitoba Medical Services Foundation (MMSF) Operating Grant to the P.I., Dr. Gillian Alcolado.

Budget Details:
PERSONNEL REQUIRED:

1) Study Coordinator, TBD
Role: Assist with writing (ethics), study management, recruitment, reminder calls, MINI assessments, preparation of group materials, assistance with knowledge translation events, data management, entry, data analyses, drafting sections of manuscripts, preparing findings for conference presentations

2) Research Assistant, TBD
Role: Assist with data entry, MINI assessments, preparation of group materials, assistance with knowledge translation events, drafting sections of manuscripts, prepating findings for conference presentations

8 hours per week (for each position). Salary ($9152) + 18% benefits ($1647.36) = $10,799.36 x 2 = Grand total of $21,598.72.
Having two personnel on this study, with one overseeing the execution, and both being able to assist with conducting assessments and data entry will allow for timely study completion.

EQUIPMENT REQUIRED:

Dell 7490 Laptop ($1611) x 2 = $3,222. Each Research Assistant will be provided with a password-protected laptop for data entry of hard copy measures, data storage, and statistical analysis.

SPSS Statistics Premium License ($140) x 3 (people) x 2 (years) = $840. Research assistants and the PI will have this statistical software package loaded onto their computers for ease of access to data for entry and analysis. Because the license year runs September-August, two years' worth of licensing will be required over the course of this study.

16GB Encrypted USB = $86.31. For transfer of de-identified data among laptops securely.

Digital Audio Recorder ($57.96) x 2 = 115.92. For audio recording of MINI assessments and BEI for purposes of reliability coding.

SUPPLIES AND SERVICES:
Consent Form Photocopies: 10 cents per page, 4 pages per consent form x 58 participants = $23.20

MINI Photocopies: 10 cents per page, 41 pages x 58 participants = $237.80 (note this interview is free for purchase to researchers whose grants are valued at less than $50,000).

Demographic Questionnaire Photocopies: 10 cents per page, 3 pages x 58 participants = $17.40

Four Assessment Outcome Measures Photocopies:
Post-Delivery Perceived Stress Inventory (PPSI): 10 cents per page x 2 pages x 4 visits x 58 participants = $46.40

Maternal Postnatal/Antenatal Attachment Scale (MPAS/MAAS): 10 cents per page x 3 pages total x 4 visits x 58 participants = $69.60

Maternal Efficacy Questionnaire (MEQ): 10 cents per page x 2 pages x 4 visits x 58 participants = $46.40

Perceived Stress Scale (PSS): 10 cents per page x 1 page x 4 visits x 58 participants = $23.20

Edinburgh Postnatal Depression Scale (EPDS): 10 cents per page x 2 pages x 4 visits x 58 participants = $46.40

Perinatal Anxiety Screening Scale (PASS): 10 cents per page x 2 pages x 4 visits x 58 participants = $46.40

Weekly Outcome Questionnaire Photocopies:
10 cents per page x 5 pages (EPDS + PASS 2 pages each, PSS 1 page) x 58 participants x 6 time points = $174

TAAS Questionnaire Photocopies: 10 cents per page, 2 pages x 58 participants = $11.60

TSM Questionnaire Photocopies: 10 cents per page, 2 pages x 58 participants = $11.60

Statistical Consulting Services: University of Manitoba Statistics Department $100 per hour x 10 hours = $1,000. Consulting services regarding analytical approach with an intent to treat analysis, carrying time points forward and controlling for missing data and other appropriate confound variables.

Participant Reimbursement: All participants will receive $10 per visit for their assessment visits, of which there are four for each condition ($10 x 4 assessments x 58 participants = $2320).

Newspaper Advertisement: $750 x 3 = $2,250.00. Based on a quotation from The Winnipeg Free Press at the University of Manitoba special rate, this allows for an ad to be run 3 times in the city newspaper in case help is needed with recruitment.

TOTAL AMOUNT: $32,186.95

Ethical Considerations

Potential benefits to subjects and others:
The potential benefits are not only for the mental and physical health of the pregnant or postpartum women, but also on their fetuses and the physical and mental health of their children.

It is hoped that this study will be of *benefit to subjects* by providing them with a novel treatment which may have the ability to enhance their understanding of perinatal anxiety and provide increased treatment gains over traditional treatments. This may involve both mental and physical health benefits directly to the mother, as well as mental and physical health benefits to their fetus' and children. Additionally, it is hypothesized that the decrease in symptoms from treatment will cause an increase in patient functionality, which will be of benefit to participants.

It is hoped that this study will also be of *benefit to others* in two key ways.

1. Practical benefits: This project (if results are as predicted) will allow the solidification of this new program patients with perinatal anxiety, first in our clinic and ultimately for others, through dissemination of these research findings.
2. Theoretical benefits: If the proposed treatment of perinatal anxiety is found to be effective, it will have important implications for our understanding of the etiology and maintenance of perinatal anxiety symptoms.

Potential harm to subjects and others:

There are a few areas of potential harm to be discussed.

1. It is possible that participants will experience discomfort, i.e., increased anxiety, during the treatment sessions as they discuss and complete exercises related to their anxiety and worries. If the participant becomes too distressed by the treatment, it will immediately be stopped, the participant will not leave the clinic until they have been debriefed and their mood has stabilized. We will make every effort to offer alternative treatment within our service, if appropriate, and make other recommendations if not.
2. Participants may fail to respond to treatment, or to experience worsening of their symptoms. These harms will be minimized by reminding participants that they are free to discontinue their participation in the study at any time to pursue other treatments. Further, participants will be offered alternative treatments at the end of the study, so they are made aware of alternative/additional treatment options.
3. It is possible that a patient could become suicidal during assessment/treatment. Participants who have pre-existing severe suicidal ideation will be exclude from the study and offered alternate resources, but those who prove to be at risk will be monitored at

every session by inquiring about their suicidal thoughts and plans, just as any therapist would in a regular clinical treatment setting. Participants at acute risk of suicide will be personally accompanied to the nearest emergency room or crisis response centre if needed.

4. Therapy session and assessments will be conducted using videoconferencing. Questionnaires will be completed electronically All videoconferencing and electronic platforms, including email, have an inherently higher risk of confidentiality breaches than in-person services. However, both Microsoft Teams and Zoom Professional have been approved for the delivery of health care services by the Winnipeg Regional Health Authority and Shared Health Services. Similarly, Survey Gizmo, our online software, is secure and approved for research.

Please note we anticipate a very low likelihood of any of these negative events, given that none of these circumstances (distress during treatment, worsening of symptoms, or increase in suicidality) occurred during the pilot study.

If this treatment is not demonstrated to be effective at reducing symptoms, it will no longer be administered to our other patients, nor will the techniques be disseminated with other clinicians for use with their patients. Thus, there are no potential harms to others beyond the study participants.