Targeting Intolerance of Uncertainty During Pregnancy:

A Randomized Controlled Trial to Prevent Postpartum Anxiety Disorders

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Abstract

Objective: Postpartum anxiety is common, often underrecognized, and associated with numerous negative outcomes for both the perinatal individual and their infant. Despite its high prevalence and burden, research focused on preventative strategies for postpartum anxiety remains very limited. This study investigated whether a 6-week cognitive behavioral therapy protocol targeting intolerance of uncertainty (CBT-IU) during pregnancy could reduce risk for postpartum anxiety disorders among individuals with heightened intolerance of uncertainty (IU).

Methods: In this investigator-initiated, single-site, proof-of-concept, randomized controlled trial (RCT), eligible participants (n = 37), between 14 and 32 weeks' gestation, with heightened IU (baseline score of ≥64 on the 27-item Intolerance of Uncertainty Scale) were randomized to a 6-session individual CBT-IU or care as usual (CAU), of whom 35 completed measures and were included in analyses. The primary objective of this study was to evaluate whether CBT-IU for pregnant individuals with elevated IU could reduce the risk of postpartum anxiety disorder compared to CAU. Secondary outcomes included changes in worry, depression, and emotion regulation.

Results: CBT-IU significantly reduced the risk of postpartum anxiety disorder onset compared to CAU ($P < .001$), with none of the participants in the CBT-IU group meeting diagnostic (or provisional) criteria for an anxiety or related disorder, compared to 31.6% of participants in the CAU group. CBT-IU participants showed clinically significantly reductions in IU ($P = .003$), worry symptoms ($P < .001$), emotion dysregulation ($P = .018$), and interviewer-rated anxiety symptoms ($P < .001$) compared to CAU. Treatment satisfaction among CBT-IU participants was high.

Conclusion: These findings suggest that targeting IU during pregnancy may be an effective preventive strategy for reducing the risk of postpartum anxiety disorder onset. This proof-of-concept RCT supports a large-scale RCT to ultimately test CBT-IU as an effective intervention for prevention of postpartum anxiety disorders.

Trial Registration: ClinicalTrials.gov identifier: NCT05691140.

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Anxiety disorders are the most common mental health conditions diagnosed during perinatal period. Prevalence studies, which typically define the perinatal period as pregnancy through 6 months postpartum, estimate rates between 15% to 25%.[1–3] The perinatal period is a time of increased psychological vulnerability[4–6] and is associated with a range of adverse maternal and infant outcomes. Perinatal individuals with anxiety disorders are at an increased risk of obstetric complications,[7–10] substance use disorders, chronic mental health difficulties, and increased suicidality.[11,12] Perinatal anxiety has also been linked to worse parent-infant bonding[13,14] and poorer infant outcomes, including less secure attachment and more difficult temperament.[15,16] Further, infants exposed to perinatal anxiety may face developmental challenges, including motor and cognitive delays, reduced attention,[10,17–20] and increased negative affect and mental health difficulties that span from infancy to adolescence.[19,21–23]

Despite the high prevalence of anxiety disorders during the perinatal period and their associated negative outcomes, less than 20% of these individuals receive treatment.[24] Considerable research has evaluated treatments for anxiety disorders during the perinatal period, with first-line evidence-based psychological treatments, including cognitive behavioral therapy (CBT) and mindfulness-based approaches, demonstrating strong efficacy in reducing anxiety symptoms.[25,26] Pharmacological treatments, most often antidepressants, are also considered a first-line option for anxiety disorders during the perinatal period, particularly for those with moderate-to-severe symptoms or when psychotherapy is unavailable or not preferred.[27] In contrast, prevention research for anxiety disorders during the perinatal period remains extremely limited, with most prevention efforts focusing on postpartum depression. Uptake of both treatment and prevention is further hindered by challenges in identifying symptoms early and accurately. As a result, there has been increased attention on improving symptom detection, including efforts to identify potential risk factors. Among the more recently identified

Clinical Points

- Anxiety disorders are common during the perinatal period and can have significant negative impacts, yet prevention strategies are rarely studied.
- Intolerance of uncertainty (IU), commonly defined as the fear of the unknown, is a modifiable risk factor that can be targeted with cognitive behavioral therapy (CBT) strategies to prevent anxiety disorders in the postpartum.
- Clinicians should consider screening pregnant patients for elevated IU, using the 27-item Intolerance of Uncertainty Scale, as those with high IU may benefit from targeted CBT for IU to reduce risk of anxiety disorders during the postpartum.

psychological risk factors for postpartum anxiety worsening is intolerance of uncertainty (IU).[28] IU is a dispositional trait characterized by the tendency to perceive uncertain situations as threatening and distressing.[29] IU is considered a transdiagnostic risk and maintenance factor for anxiety disorders,[29–33] and individuals with elevated IU often experience heightened worry and engage in safety behaviors (eg, avoidance, reassurance seeking) in an effort to reduce uncertainty.[34–36] Increased IU is also associated with difficulties in emotion regulation, which can intensify worry and encourage reliance on safety behaviors, further amplifying distress.[37–39] Emotion dysregulation has also been linked to anxiety during the perinatal period[40,41] and has been shown to mediate the relationship between IU and worry in nonperinatal populations,[42] suggesting that interventions targeting IU may also improve emotion regulation. Further, IU has been identified as an important mechanism in CBT outcomes. Research suggests that reductions in IU are associated with reductions in anxiety and worry symptoms, suggesting that IU may act as both a predictor and mediator of treatment response.[43–45] CBT protocols specifically targeting IU have demonstrated strong effectiveness in the treatment of generalized anxiety disorder (GAD) in nonperinatal populations.[35,46–49] More recently, studies have demonstrated that CBT for IU protocols is significantly more effective at reducing both IU and worry symptoms when compared to general CBT protocols for individuals with GAD.[33]

The perinatal period is inherently characterized by increased uncertainty across various domains, including uncertainty about childbirth, the health of the baby, shifts in personal identity and relationships, and the ability to manage the physical and emotional demands of parenting. For individuals with heightened IU, this inherent uncertainty may potentially amplify distress and increase vulnerability to anxiety. Elevated IU has been shown to predict anxiety worsening in the postpartum,[28] fear of childbirth,[50,51] and poorer psychological well-being during pregnancy.[52,53] Further, reductions in IU have been shown to mediate improvements in anxiety among perinatal individuals receiving CBT.[54] Given the inherent uncertainty of the perinatal period and the identification of IU as a risk factor for postpartum anxiety worsening, this proof-of-concept randomized controlled trial (RCT) aimed to evaluate whether a CBT protocol targeting IU during pregnancy could reduce the risk of anxiety disorders during the postpartum period. The primary objective of this study was to evaluate whether a 6-session individual CBT protocol targeting IU (CBT-IU) for pregnant individuals with elevated IU could reduce postpartum anxiety disorder risk, compared to care as usual (CAU). We hypothesize that participants who engage in CBT-IU will experience significant reductions in IU and anxiety symptoms, as well as a decreased risk of developing an anxiety disorder during the postpartum period compared to those receiving CAU.

METHODS

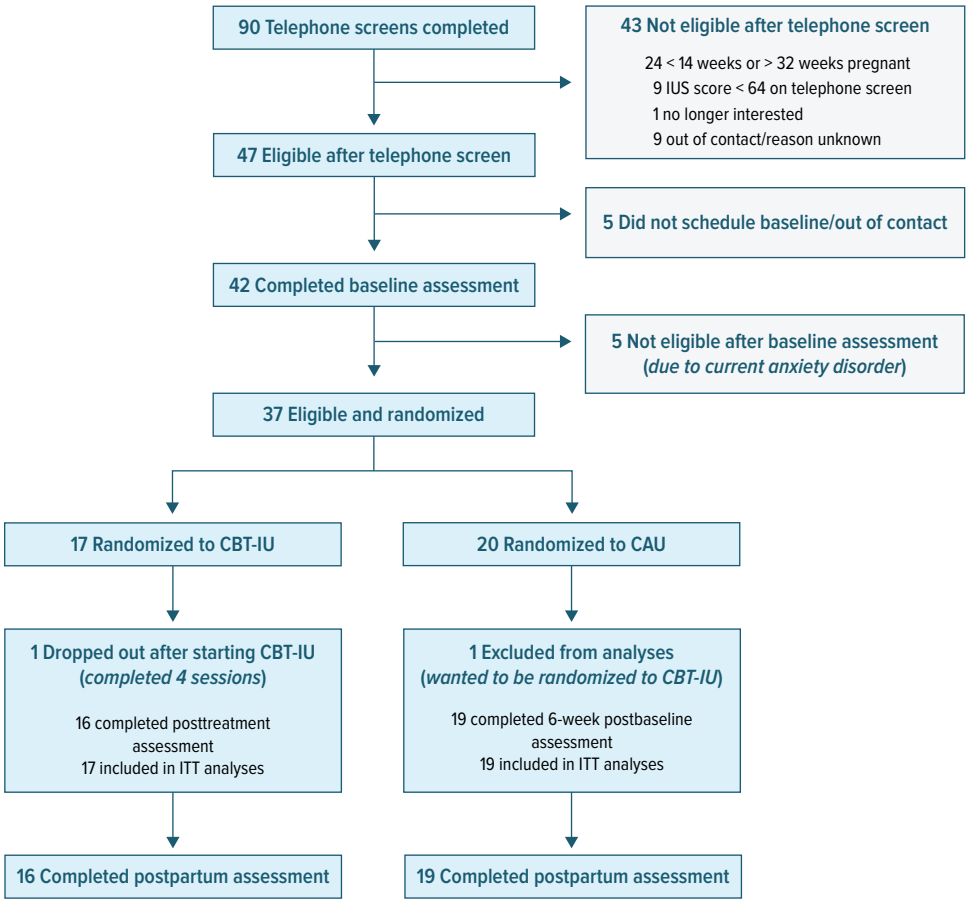
An investigator-initiated, single-site, proof-of-concept, RCT (ClinicalTrials.gov identifier: NCT05691140) was conducted at the Women's Health Concerns Clinic (WHCC), St. Joseph's Healthcare Hamilton, a university affiliated teaching hospital clinic in Hamilton, Ontario, Canada. The study protocol was approved by the Hamilton Integrated Research Ethics Board (HiREB #13902), in accordance with the Declaration of Helsinki. All participants provided written informed consent before study entry. Please refer to Furtado et al[55] for a detailed description of the study protocol.

Participants

Eligible participants were recruited from the Greater Hamilton and surrounding area between October 2022 and August 2024 through online advertisements and postings within the community (eg, midwifery, family physician, and obstetric clinics). Inclusion criteria were as follows: (1) pregnant individuals (between 14 and 32 weeks' gestation); (2) 18 years or older; (3) a baseline score of 64 or greater on the Intolerance of Uncertainty Scale (IUS)[56]; (4) no current psychotropic medication use or, if taking medication, no change in dose or type for a minimum of 6 weeks prior to baseline (nonpsychotropic medications were permitted); (5) no concurrent psychological treatment during pregnancy (after the baseline visit); and (6) fluent in English and able to consent for treatment. Exclusion criteria were (1) current diagnosis of a *DSM-5*[57] anxiety disorder at baseline; (2) current major depressive episode; (3) actively suicidal at baseline; and/or (4) diagnosed with a psychotic disorder or current substance or alcohol use

Figure 1.

Flowchart of Participants' Screening, Eligibility, and Study Procedures[a]



Abbreviations: CBT-IU = cognitive behavioral therapy of intolerance of uncertainty, CAU = care as usual, ITT = intent to treat, IUS = Intolerance of Uncertainty Scale.

disorder. Please see Figure 1 for a flowchart outlining participant screening, eligibility, and study procedures.

Study Design

Following the study screening process, participants engaged in a baseline assessment where informed consent was reviewed and provided. Psychiatric diagnoses were determined at baseline using the Mini-International Neuropsychiatric Interview for *DSM-5* version 7.0.1 (MINI). If participants were ineligible at baseline due to an anxiety and/or mood disorder, they were offered the opportunity to receive psychological services (eg, CBT groups) through our clinic. Participants who were excluded for other types of disorders (eg, substance use disorder) were provided with appropriate resources and, if desired, referrals to treatment at other clinics. Eligible participants were then randomly assigned to CBT-IU or CAU using block randomization, with a computer-generated assignment sequence that was prepared prior to the start of the study. A battery of symptom assessment measures was administered within 2 weeks post–CBT-IU completion or within 2 weeks following the control period (eg, 6–8 weeks postbaseline for CAU participants) and again between 6–12 weeks postpartum. At the postpartum visit, the anxiety and related disorders (eg, obsessive-compulsive disorder, posttraumatic stress disorder [PTSD]) MINI modules were readministered.

If participants randomized to CAU exhibited clinically significant symptoms of an anxiety and/or related disorder at the postcontrol and/or postpartum visit(s), they were offered clinical care within the WHCC, as needed. For those randomized to CBT-IU, if clinically significant symptoms were present at the postpartum visit, the same resources would be offered. To ensure accessibility for all participants who may not have been able to attend in-person visits, all study visits were completed virtually via the Zoom Video Communications platform. To reduce attrition, all participants were compensated following each assessment time point with a $20 e-gift card.

Table 1.
Schedule of Study Measurements

Procedures and measures	Baseline	Posttreatment	Postpartum
Enrollment			
Informed consent	X		
Randomization	X		
Structured interview			
MINI for *DSM-5*	X		
Primary outcomes			
MINI modules[a]	X		X
Intolerance of Uncertainty Scale	X	X	X
Secondary outcomes			
Hamilton Anxiety Rating Scale	X	X	X
Generalized Anxiety Disorder 7-item Scale	X	X	X
Edinburgh Postnatal Depression Scale	X	X	X
Penn State Worry Questionnaire	X	X	X
Difficulties in Emotion Regulation Scale	X	X	X
Posttraumatic Stress Disorder Checklist for *DSM-5*[b]	X	X	X
Client Satisfaction Questionnaire[c]		X	
Other factors			
Demographics and medical history	X		
Obstetric information	X		X

[a]Postpartum anxiety prevention is assessed through use of the anxiety and related disorders MINI modules.
[b]Only completed by participants endorsing a criterion A trauma at baseline or postpartum (related to traumatic childbirth).
[c]Only completed by participants in the CBT-IU group.
Abbreviations: CBT-IU = cognitive behavioral therapy of intolerance of uncertainty, MINI = Mini-International Neuropsychiatric Interview for *DSM-5*.

Study Arms

CBT-IU for postpartum anxiety prevention. Participants randomized to CBT-IU received treatment in an individual format with 1 of 2 trained, senior level PhD clinical psychology students (M.F. or B.E.I.), supervised by a licensed clinical psychologist (S.M.G.). The CBT-IU protocol consisted of six 1-hour virtual sessions that took place weekly during pregnancy and beginning within 2 weeks of completing their baseline assessment. Participant worksheets such as worry monitoring forms, behavioral experiment logs, and imaginal exposure logs were developed based upon previous CBT for IU protocols, which have only been used in nonperinatal populations,[35,47,48,58] as well as a CBT for perinatal anxiety protocol (primary use was for perinatal anxiety psychoeducation content[59]). These session worksheets were used during weekly sessions with participants, as well as between sessions as part of participants' CBT home practice. CBT-IU aimed to reduce IU through psychoeducation focusing on anxiety during the perinatal period, the role of IU, and how IU impacts thoughts, emotions, and behaviors. Throughout sessions, participants learned and engaged in behavioral experiments, imaginal exposure, and problem-solving training to challenge negative beliefs and safety behaviors associated with IU. Please refer to Furtado et al[55] for an overview of the complete session-by-session content.

Care as usual. The CAU study arm served as the control condition in this study, in which participants were not assigned to any type of study intervention. To closely resemble real-world settings, participants in CAU would not be excluded from the study analyses if they initiated psychological and/or psychopharmacological treatment during the study (following baseline). Any treatments that were initiated by participants following the postcontrol time point were recorded at the postcontrol and postpartum visits. If participants in the CAU group were to experience any distressing mental health symptoms (eg, anxiety, depression), they were asked to notify the first author to ensure that access to appropriate services was provided within the WHCC (eg, group CBT).

Study Measures

The study assessment battery consisted of interviewer-rated and self-report measures of IU, anxiety, worry, and depressive symptoms, as well as measures assessing emotion regulation, traumatic stress, and treatment satisfaction. Refer to Table 1 for a list of study measures and their associated timing.

Primary outcomes. The anxiety and related disorders MINI modules were readministered at the postpartum time point to assess the primary outcome of postpartum anxiety prevention. Specifically, MINI diagnostic modules for anxiety disorders, as well as anxiety-related disorders (eg, obsessive-compulsive disorder, PTSD, *in relation to traumatic childbirth experiences*), were administered. If participants were reporting other potentially relevant clinical symptoms (eg, low mood), associated diagnostic modules were administered to confirm the presence of any other *DSM-5* diagnoses during postpartum. Prevention of

postpartum anxiety was defined for those participants who did not meet a diagnosis of any of the aforementioned anxiety or anxiety-related disorders at the postpartum time point. Given the length of symptom duration (ie, minimum of 6 months) necessary to meet diagnostic criteria for specific anxiety disorders (eg, GAD), we used *provisional* diagnostic criteria as participants were followed up to 12 weeks postpartum. Specifically, participants must have fulfilled all other *DSM-5* criteria, particularly whether symptoms experienced were significantly distressing and/or impairing functioning, to meet for a provisional postpartum diagnosis of such disorders. Changes in IU were measured with the 27-item IUS, with higher scores indicating greater IU.[60,61]

Secondary outcomes. The Hamilton Anxiety Rating Scale[62] (HAM-A) is a 14-item, interviewer-administered tool designed to assess overall anxiety severity and is widely recognized as a gold-standard measure. The Generalized Anxiety Disorder 7-Item Scale[63] (GAD-7) is a self-report measure assessing anxiety severity over the past two weeks, with higher scores indicating greater severity. The Edinburgh Postnatal Depression Scale[64] (EPDS) is a 10-item self-report measure of perinatal depression symptoms, with higher total scores indicating greater symptom severity. The Penn State Worry Questionnaire[65] (PSWQ) is a 16-item self-report measure of pathological worry, with higher scores reflecting greater worry symptoms. The Difficulties in Emotion Regulation Scale[66] (DERS) is a 36-item self-report measure assessing six emotion regulation dimensions: nonacceptance, goals, impulse, awareness, strategies, and clarity, with higher scores indicating greater difficulties in emotion regulation. The Posttraumatic Stress Disorder Checklist for *DSM-5*[67] (PCL-5) is a 20-item self-report measure assessing PTSD symptoms. In the present study, the PCL-5 was only administered to participants who reported a criterion A trauma at baseline or postpartum, as assessed by the MINI.

Client satisfaction with treatment. The Client Satisfaction Questionnaire[68] (CSQ) is an 8-item self-report measure assessing client satisfaction with health services. Items are rated on a 4-point Likert scale (1–4), with higher total scores reflecting greater satisfaction with services. Only participants assigned to CBT-IU completed the CSQ to assess satisfaction with the treatment protocol.

Other factors. Information pertaining to participants' age, gender identity, race, marital status, parity, education level, and current medications was collected at baseline. At the postpartum visit, participants were asked about medication use, as well as whether they had engaged in any psychotherapeutic interventions during the postpartum period, and these were added as covariates to the analyses.

Statistical Analysis

Participants in CBT-IU and CAU were compared on baseline clinical and demographic characteristics using χ^2 or independent sample *t* tests. To assess the primary outcome of postpartum anxiety prevention, a χ^2 test was used to compare the proportion of participants meeting diagnostic criteria for an anxiety and/or related disorder between CBT-IU and CAU. A modified intention-to-treat (ITT) approach was used, in which participants who did not complete any self-report baseline measures were excluded (n = 1). Linear mixed models were used to examine changes in primary (eg, IUS) and secondary outcomes over time between CBT-IU and CAU, where the model included fixed effects for group (CBT-IU vs CAU), time (eg, baseline, posttreatment/control, postpartum), and their interaction (group × time). Medication use for mental health concerns and psychotherapy use during the postpartum were included as a covariate. For outcomes with a significant group × time interaction, post hoc pairwise comparisons using Bonferroni adjustment were conducted to examine changes between specific time points for each group. Partial eta-squared (η^2_p) was computed to estimate effect sizes, with values of 0.01, 0.06, and 0.14 interpreted as small, medium, and large effects, respectively. All statistical tests were 2-tailed with a significance level set at $P < .05$. Statistical analyses were conducted using IBM SPSS Statistics (version 29).[69]

Table 2.

Baseline Demographic and Clinical Characteristics by Group

Baseline characteristics	CBT-IU (n = 17)[a]	CAU (n = 20)[a]	*P* value (t/χ^2)
Age, mean (SD), y	31.43 (2.74)	33.11 (3.91)	.18
Gestational weeks, mean (SD)	26.76 (4.71)	25.10 (5.56)	.338
Race			
Black	0 (0)	2 (10)	.21
East Asian	0 (0)	2 (10)	
South Asian	0 (0)	1 (5)	
West Asian	1 (5.9)	0 (0)	
White	16 (94.1)	15 (75)	
Marital status			.25
Single	0 (0)	2 (10)	
Married	16 (94.1)	15 (75)	
Common law	1 (5.9)	3 (15)	
Education level			.08
High school	0 (0)	2 (10)	
College/diploma	4 (23.5)	0 (0)	
University/degree	7 (41.2)	8 (40)	
Postgraduate	6 (35.3)	10 (50)	
Parity			.82
Primigravida	10 (58.8)	11 (55)	
Multigravida	7 (41.2)	9 (45)	

[a]Data are presented as n (%) of participants, unless otherwise indicated.
Abbreviations: CBT-IU = cognitive behavioral therapy of intolerance of uncertainty, CAU = care as usual, *t* = *t* test, χ^2 = chi-square test of difference between groups.

RESULTS

A total of 42 participants completed the study baseline screening assessment, 5 of which were deemed ineligible

Table 3.

Linear Mixed Model Comparing CBT-IU (n = 16) to Care as Usual (n = 19) on Outcomes From Baseline to Postpartum

	CBT-IU			CAU						
	Baseline mean (SD)	Posttreatment mean (SD)	Postpartum mean (SD)	Baseline mean (SD)	Post-CAU mean (SD)	Postpartum mean (SD)		*F* value	*P* value	η^2_p
IUS	82 (9.9)	64.5 (20.5)	64.9 (19.5)	75.5 (10.9)	71.4 (13.9)	69.9 (18.3)	Time	11.93	<.001	.16
							Group × time	6.53	.003	
HAM-A	11.7 (4.8)	7.4 (4.4)	5.7 (2.6)	9.5 (3.9)	14.32(5.5)	9.95 (4.1)	Time	5.52	.006	.28
							Group × time	12.76	<.001	
PSWQ	60 (7.8)	50.4 (7.4)	51.3 (11.5)	58.1 (7.1)	59.1 (7.2)	57 (9.8)	Time	7.03	.002	.22
							Group × time	9.47	<.001	
GAD-7	8 (4.2)	5.3 (2.7)	5.6 (4.4)	7.6 (3.9)	7.7 (3.9)	6.9 (5.4)	Time	1.41	.251	.06
							Group × time	2.23	.115	
EPDS	8.19 (3.4)	7.31 (3.9)	5.69 (3.3)	8.74 (4.9)	8.95 (4.5)	7.42 (4.)	Time	2.25	.113	.01
							Group × time	0.44	.645	
DERS	84.4 (14.5)	73.7 (14.2)	67.1 (17.1)	86.4 (18.9)	83.8 (14.8)	81.84 (18.3)	Time	6.58	.002	.11
							Group × time	4.27	.018	

Abbreviations: CAU = care as usual, CBT-IU = Cognitive Behavioral Therapy for Intolerance of Uncertainty, DERS = Difficulties in Emotion Regulation Scale, EPDS = Edinburgh Postnatal Depression Scale, GAD-7 = Generalized Anxiety Disorder 7-Item Scale, HAM-A = Hamilton Anxiety Rating Scale, IUS = 27-Item Intolerance of Uncertainty Scale, PSWQ = Penn State Worry Questionnaire, SD = standard deviation.

due to meeting current diagnostic criteria for a *DSM-5* anxiety disorder. Following randomization of our 37 participants, 1 participant randomized to CAU declined further participation (due to wanting to be randomized to CBT-IU) and did not complete the baseline self-report measures (aside from the IUS used to determine eligibility), and, as such, they were excluded from the analyses. This resulted in a modified ITT sample of 36 participants (mean age = 32.4 years, SD = 3.5, range = 25 to 38). One participant in the CBT-IU group discontinued participation in the study following 4 CBT-IU sessions, due to a family emergency that prevented them from actively engaging. As such, they were unable to complete the remaining study visits, including the postpartum visit in which we assessed for anxiety and related disorders. This participant was therefore excluded from our primary outcome (postpartum anxiety disorder) analyses, as we were unable to assess for the presence of any anxiety and/or related disorders in the postpartum period. All other CBT-IU participants completed the full course of treatment (6 sessions). Two participants in each group (CBT-IU and CAU) had a history of an anxiety disorder, which had been in full remission for an average of 3 years at the start of the study. There were no significant differences between groups on baseline demographic and clinical characteristics (see Table 2). At the postpartum time point, no participants endorsed a Criterion A index trauma related to childbirth.

Primary Outcomes

A χ^2 test of independence was conducted to examine the relationship between groups (CBT-IU and CAU) and postpartum outcome (presence of anxiety and/or related disorder). The results indicated that there was a significant relationship between group and postpartum outcome ($\chi^2_{1,35} = 6.098$, $P = .014$), suggesting that participants in the CAU group were significantly more likely to meet diagnostic (or provisional) criteria for an anxiety disorder during the postpartum period compared to participants in the CBT-IU group. Of the 16 CBT-IU participants who completed their postpartum assessment, none (0%) met diagnostic (or provisional) criteria for an anxiety and/or related disorder. One (6.3%) CBT-IU participant met criteria for current major depressive disorder, peripartum onset, and was offered services within our clinic. Of the 19 CAU participants, 6 (31.6%) met diagnostic (or provisional) criteria for an anxiety disorder. Specifically, 2 participants met diagnostic criteria for social anxiety disorder, and 4 met provisional diagnostic criteria for GAD in the postpartum. Of the CAU participants meeting diagnostic (or provisional) criteria for an anxiety disorder, 3 had begun medication or psychotherapy specific for anxiety occurring in the postpartum. All were offered services within our clinic. The CBT-IU group also exhibited significantly greater reductions in IU (IUS; $F_{2,66.97} = 6.53$, $P = .003$, $\eta^2_P = .16$) both following completion of CBT-IU and at the 6–12 week postpartum visit, as compared to CAU (Table 3). Post hoc pairwise comparisons indicated significant reductions from baseline to posttreatment (MD = 17.45, SE = 3.70, $P < .001$) and baseline to postpartum (MD = 20.73, SE = 4.02, $P < .001$), with no significant change between posttreatment and postpartum ($P > .05$), suggesting that treatment gains

were maintained. In contrast, CAU participants showed no significant changes across time points ($P > .05$).

Secondary Outcomes

There were significantly greater reductions in the CBT-IU group for self-reported worry (PSWQ; $F_{2,66.40} = 9.47$, $P < .001$, $\eta^2_P = .22$), with post hoc comparisons showing significant reductions from baseline to posttreatment (MD = 9.33, SE = 2.05, $P < .001$) and baseline to postpartum (MD = 9.84, SE = 2.15, $P < .001$), with no significant change from posttreatment to postpartum ($P > .05$), suggesting gains in worry reduction were maintained in the CBT-IU group. The CAU group showed no significant changes across time points ($P > .05$). Significantly greater reductions in the CBT-IU group for emotion regulation symptoms (DERS; $F_{2,66.39} = 4.27$, $P = .018$, $\eta^2_P = .11$) were also observed compared to CAU. Post hoc comparisons indicated that the CBT-IU group experienced significant reductions from baseline to posttreatment (MD = 10.18, SE = 3.58, $P = .024$) and baseline to postpartum (MD = 17.64, SE = 3.75, $P < .001$), with no significant change from posttreatment to postpartum ($P > .05$). The CAU group showed no significant changes across time points ($P > .05$). There were no significant differences between groups in self-reported anxiety (GAD-7) and depressive (EPDS) symptoms. With respect to interviewer-rated anxiety (HAM-A), there was a significantly greater reduction in anxiety symptoms in CBT-IU compared to CAU ($F_{2,\ 67.35} = 12.76$, $P < .001$, $\eta^2_P = .28$), with post hoc comparisons suggesting significant reductions from baseline to posttreatment (MD = 4.33, SE = 1.23, $P = .004$) and baseline to postpartum (MD = 6.72, SE = 1.28, $P < .001$). No significant changes were observed in CBT-IU from posttreatment to postpartum ($P > .05$), suggesting that reductions in anxiety were maintained. In the CAU group, HAM-A scores increased significantly from baseline to postcontrol (MD = 4.73, SE = 1.40, $P = .005$) and then decreased from postcontrol to postpartum (MD = 3.87, SE = 1.50, $P = .042$). Refer to Table 3.

Treatment Satisfaction

One participant in CBT-IU did not complete the CSQ due to an error in delivering the electronic questionnaires. Participants in CBT-IU were highly satisfied with the treatment received (CSQ, mean = 29.73, SD = 3.15). All CBT-IU participants rated the treatment as "excellent" (86.7%, n = 13) or "good" (13.3%, n = 2). Participants also reported that CBT-IU helped them cope "better" (33.3%, n = 5) or a "great deal better" (66.7%, n = 10) with their symptoms, and participants reported being "very satisfied" (73.3%, n = 11) or "mostly satisfied" (26.7%, n = 4) with the treatment. All participants (100%, n = 15) reported that they would recommend CBT-IU to others.

DISCUSSION

Anxiety disorders during the perinatal period are common, often underrecognized, and associated with numerous adverse outcomes for both the perinatal individual and infant. To date, most of the research has focused on the use of interventions in which anxiety is addressed after symptoms have emerged and led to clinical distress and impairments in day-to-day functioning, with little to no research focusing on preventing anxiety disorders before they develop. Our findings provide preliminary evidence that CBT-IU reduces the onset of anxiety disorders in the postpartum as none of the participants in the CBT-IU group met diagnostic (or provisional) criteria for an anxiety and/or related disorder in the postpartum, compared to 31.6% of participants in the CAU group. Additionally, participants in the CBT-IU group experienced significantly greater reductions in IU compared to those in CAU at both the posttreatment and postpartum follow-up visits. These group differences are clinically meaningful and suggest that targeting IU during pregnancy may reduce the likelihood of developing an anxiety disorder in the postpartum, a period known to be associated with increased vulnerability to mental health difficulties.[4–6]

CBT-IU was also associated with significantly greater reductions in worry symptoms, as measured by the PSWQ. Research has shown that IU is highly associated with worry in both clinical and nonclinical populations and both share common features regarding uncertainty and uncertainty-induced safety behaviors.[32,43,60] By learning to respond to uncertainty with greater flexibility and tolerance and less avoidance and rumination, participants may have been less likely to experience distressing worry, including in the postpartum period, when more uncertainly naturally exists. This aligns with research in nonperinatal populations showing that CBT protocols targeting IU are particularly effective for reducing both IU and worry.[33,49] Participants in the CBT-IU group also exhibited significantly greater reductions in interviewer-rated anxiety symptom severity, as measured by the HAM-A. Through CBT-IU strategies, such as behavioral experiments and imaginal exposure, participants repeatedly practice tolerating uncertainty and learn that worry and excessive safety behaviors are not necessary to prevent negative outcomes. As such, participants likely experienced both cognitive and somatic anxiety reductions, both of which are captured with the HAM-A. Interestingly, group differences did not emerge for self-reported anxiety (GAD-7), despite significant differences between groups on the HAM-A. This discrepancy may reflect differences in how these measures assess anxiety symptoms. The HAM-A is a clinician-rated and structured measure, allowing for probing and clarification to ensure accurate scoring, whereas the GAD-7 is a self-report measure based

specifically on *DSM* criteria for GAD and may be less sensitive to subtle changes. Additionally, the HAM-A captures a broader spectrum of anxiety symptoms, including both cognitive and somatic features, such as physical symptoms related to anxiety (eg, cardiovascular, gastrointestinal). Individuals with increased IU tend to experience greater autonomic arousal in uncertain situations,[70] which may be better captured by the HAM-A, as it assesses a broader range of anxiety symptoms compared to the GAD-7. As such, the GAD-7 may be less sensitive to the somatic symptoms of anxiety, which could help explain why significant group differences were observed on the HAM-A, but not the GAD-7. Baseline GAD-7 scores were also relatively low, leaving little room for improvement, whereas HAM-A scores, though mild, were higher, allowing the potential for greater observable change. Nevertheless, it is not entirely clear why group differences emerged on the HAM-A but not the GAD-7, especially given that other related measures, such as the PSWQ, did show significant improvements. Future research is needed to clarify how different anxiety measures may capture treatment-related changes in the perinatal context.

Emotion dysregulation also significantly decreased in the CBT-IU group compared to CAU, as measured by the DERS. Emotion dysregulation is a known transdiagnostic factor in the development and maintenance of anxiety disorders,[71,72] and recent research has also demonstrated its role in the perinatal period and association to perinatal anxiety.[40] Individuals with greater IU interpret uncertain situations as threatening, which can heighten anxiety and reliance on maladaptive emotion regulation strategies, such as reassurance-seeking and thought suppression.[38] By targeting IU directly, CBT-IU may reduce the perceived threat of uncertainty, thereby decreasing the need for unhelpful emotion regulation strategies. As individuals build greater tolerance for uncertainty and the distress it evokes, they may be become better equipped to engage in flexible and adaptive responses, in place of maladaptive emotion regulation strategies. This may explain why CBT-IU was more effective than CAU in reducing emotion dysregulation. Although CBT-IU was effective in reducing IU, anxiety, worry, and emotion dysregulation, it did not lead to significant reductions in depression scores (EPDS) compared to CAU. One likely explanation is that the CBT-IU protocol did not directly target depression symptoms, as it focused primarily on addressing IU. Additionally, baseline depression scores in our sample were relatively low, which may have limited the potential for observable changes. Lastly, high treatment satisfaction among CBT-IU participants further underscores its feasibility and acceptability. All participants endorsed the treatment as helpful, with the majority rating it as "excellent" and stating that they would recommend it to others. These results suggest that pregnant individuals with heightened IU who may be at risk of postpartum anxiety are not only willing to engage in a brief intervention but also perceive it as valuable and effective.

Limitations

There are some limitations that should be considered when interpreting these findings. The sample size was relatively small and primarily composed of individuals from similar demographic backgrounds, which may limit generalizability. This is important, given research that lower education and socioeconomic disadvantage are associated with increased risk of anxiety disorders during the perinatal period.[73,74] This highlights the need to replicate these findings in more diverse sociodemographic groups to better understand the role of IU and the effectiveness of CBT-IU across more diverse perinatal populations. As this was a proof-of-concept trial, we were interested in determining initial evidence of effectiveness of CBT-IU in reducing the risk of postpartum anxiety disorder onset. The follow-up period was limited to 6–12 weeks postpartum, a timeframe chosen for feasibility, to reduce attrition, and to capture early-onset anxiety disorders. It is important to note that definitions of the postpartum period vary widely in the literature, ranging from 4 weeks[75] to 3, 6, and 12 months postpartum.[1,76] Consequently, longer-term outcomes remain unknown, and, as such, we cannot determine who may recover naturally, maintain improvements, or experience worsening anxiety later in the postpartum. Future studies should include longer-term follow-ups to better understand these trajectories. Additionally, given the timeline, we used provisional diagnostic criteria for certain *DSM-5* anxiety disorders (eg, GAD), and, as such, we do not know whether full diagnostic criteria that includes the minimum 6-month duration of symptoms would be met if participants were followed. While standardized procedures were used, a limitation of this study is that assessors were not blinded to group allocation, which may have introduced a potential risk of unconscious bias. Blinding helps minimize expectancy effects and social desirability, as well as potential influence on participants' responses. Future larger, blinded trials with longer postpartum time points are needed to confirm the effectiveness of CBT-IU for preventing anxiety disorders during the postpartum. While CAU served as the comparison condition, it is not known whether CBT-IU's benefits were due to its specific components or the structured support it provided. Given that CBT-IU involved 6 individual sessions during pregnancy, nonspecific factors such as consistent support, may have contributed to reductions in IU and anxiety. Future studies would benefit from a comparison of CBT-IU to other forms of structured support (eg, psychoeducation) that provide a similar

amount of contact, but do not include active CBT-IU components, in order to better isolate the specific effects of CBT-IU. Although CBT-IU is theorized to reduce anxiety through changes in IU, this study did not directly examine IU as a mechanism of change, which should be investigated in future studies. Lastly, pregnancy and birth complications, beyond those related to Criterion A, were not systematically recorded, which may have affected participants' experiences of uncertainty. Future studies should assess these factors to better understand their potential impact.

CONCLUSION

Although postpartum anxiety is associated with a range of negative outcomes for both the individual and their infant, research to date has not focused on preventative interventions for those at increased risk of developing anxiety disorders during the postpartum period. This study provides initial evidence that targeting IU through a brief CBT protocol during pregnancy may reduce the risk of developing anxiety disorders in postpartum individuals with elevated IU during pregnancy. These findings underscore the potential of targeting psychological vulnerability factors, such as IU, to prevent the onset of anxiety during the postpartum, which is already a time marked by increased uncertainty and vulnerability. This study highlights the value of promoting prevention by providing support and tools to perinatal individuals who are at risk of developing an anxiety disorder, rather than waiting until symptoms become significantly distressing and interfering.

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