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Research paper

Internet delivered cognitive behavior therapy for antenatal depression: A randomised controlled trial☆

Erik Forsell[a,*], Marie Bendix[b], Fredrik Holländare[c], Barbara Szymanska von Schultz[d], Josefine Nasiell[e], Margareta Blomdahl-Wetterholm[h], Caroline Eriksson[f], Sara Kvarned[f], Johanna Lindau van der Linden[f], Elin Söderberg[f], Jussi Jokinen[a,b], Katarina Wide[g], Viktor Kaldo[a]

[a] Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Sweden
[b] Department of Clinical Sciences, Psychiatry, Umeå University, Sweden
[c] University Health Care Research Centre, Faculty of Medicine and Health, Örebro University, Sweden
[d] Department of Children and Women, Karolinska University Hospital, Huddinge, Sweden
[e] Department of Clinical Science, Intervention and Technology (CLINTEC), Division of Obstetrics and Gynecology, Karolinska Institutet, Sweden
[f] Department of Psychology, Uppsala University, Sweden
[g] Department of Clinical Science, Intervention and Technology (CLINTEC), Department of Pediatrics, Karolinska Institutet, Sweden
[h] Psychiatry Southwest, Stockholms Läns Sjuvårdsområde (SLSO), Stockholm, Sweden

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ABSTRACT

Major depression occurs in 5–10% of pregnancies and is associated with many negative effects for mother and child, yet treatment options are scarce. To our knowledge, this is the first published randomised controlled trial on Internet delivered Cognitive Behavior Therapy (ICBT) for this group.

Objective: To test the efficacy of a pregnancy adapted version of an existing 10-week ICBT-program for depression as well as assessing acceptability and adherence

Design: Randomised controlled trial.

Setting: Online and telephone.

Population or sample: Self-referred pregnant women (gestational week 10–28 at intake) currently suffering from major depressive disorder.

Methods: 42 pregnant women (gestational week 12–28) with major depression were randomised to either treatment as usual (TAU) provided at their antenatal clinic or to ICBT as an add-on to usual care.

Main outcome measures: The primary outcome was depressive symptoms measured with the Montgomery-Åsberg depression rating scale-self report (MADRS-S). The Edinburgh Postnatal Depression Scale and measures of anxiety and sleep were used. Credibility, satisfaction, adherence and utilization were also assessed.

Results: The ICBT group had significantly lower levels of depressive symptoms post treatment ($p < 0.001$, Hedges $g = 1.21$) and were more likely to be responders (i.e. achieve a statistically reliable improvement) (RR = 0.36; $p = 0.004$). Measures of treatment credibility, satisfaction, utilization, and adherence were comparable to implemented ICBT for depression.

Limitations: Small sample size and no long-term evaluation.

Conclusion: Pregnancy adapted ICBT for antenatal depression is feasible, acceptable and efficacious. These results need to be replicated in larger trials to validate these promising findings.

1. Introduction

For women of child bearing age depression is the leading cause of disease burden worldwide and 5–10% of all pregnant women suffer from antenatal depression (AND; Becker et al., 2016).

AND is associated with negative outcomes such as increased risk of premature delivery, decreased breastfeeding initiation (Grigoriadis et al., 2013), and poor attachment (Lefkovics et al., 2014). AND is also the strongest risk factor for postpartum depression which is associated with several negative effects for both mother and child (Vigod et al., 2016). Perinatal depression is a severe condition that needs to be identified and treated as early as possible (Vigod et al., 2016). Still

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* Correspondence to: Internetpsykiatrienheten M58, Huddinge Sjukhusområde, Huddinge, 14120 Stockholm, Sweden.
E-mail address: erik.forsell@ki.se (E. Forsell).

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there is a paucity of treatment research for antenatal depression. Though antidepressant medication is generally considered safe by clinicians, and is being used at least in severe cases[5], most women are reluctant to use them (Goodman, 2009; Vigod et al., 2016). So far no randomized controlled trial has evaluated treatment-, or fetal, effects of antidepressant medication during pregnancy.

Perinatal women seem to prefer individual therapy for depression over group therapy or medication (O'Mahen and Flynn, 2008; Goodman, 2009), and individual face-to-face CBT has been found to be effective in this group (Burns et al., 2013; O'Mahen et al., 2013a; Sockol, 2015; Milgrom et al., 2015). However, qualitative studies suggest that women perceive a lack of knowledge among health care professionals as a barrier to treatment seeking (Jarrett, 2016), and feel that psychotherapy needs to take perinatal women's specific situation into account in order to feel relevant (O'Mahen et al., 2012). This suggests that specialized treatments are warranted. Other important perceived barriers to treatment in this group are stigma, cost, lack of time, transportation, and childcare issues (Goodman, 2009; Kopelman et al., 2008; O'Mahen and Flynn, 2008). Perhaps then, making treatments available both from home, via the internet, and with relative anonymity, while adding a specific perinatal focus might be an attractive option for this group.

Internet delivered CBT with brief therapist guidance (ICBT) is effective for a variety of psychiatric disorders including depression (Andersson et al., 2008; Cuijpers et al., 2010) and can be cost-effective (Hedman et al., 2012) and implemented in routine care (Hedman et al., 2014). Postpartum depression has been targeted in four online trials so far (Danaher et al., 2013; O'Mahen et al., 2013b, 2014; Pugh et al., 2016). Two trials used weekly live or telephone sessions together with online material (Danaher et al., 2013; O'Mahen et al., 2014)' and two used a fully online approach (O'Mahen et al., 2013b; Pugh et al., 2016) similar to that described by Andersson et al. (2008). Pugh et al. (2016) used a pregnancy-adapted version of an existing ICBT-protocol while O'Mahen et al. (2013b; 2014) seem to use a pregnancy adapted ICBT protocol based on behavioral activation while not directly adapted from an existing ICBT protocol. Of the trials included in a recent systematic review (Ashford et al., 2016) however, no full-on ICBT trial that targeted pregnant women with depression has been published so far. For AND, there has been one trial on face-to-face CBT with supplementary online assistance showing promising results (Kim et al., 2014).

1.1. Study objective

This study aimed to strengthen the overall evidence for CBT for antenatal depression and specifically to test the efficacy of an ICBT program for antenatal depression.

1.2. Hypothesis

Adding ICBT to treatment as usual (TAU) will be significantly more effective than TAU alone in reducing depressive symptoms.

2. Methods

2.1. Participants

Participants were recruited by advertisements on social media websites, in blogs, online forums and newspapers. Information, posters and flyers were also distributed to maternity clinics all over Sweden. The study also featured in an article in the midwives' association's newsletter as well as a popular commercial pregnancy magazine. The study was also promoted on the website of the Internet Psychiatry Clinic in Stockholm (Hedman et al., 2014). All patients were self-referred.

2.2. Inclusion criteria

To be eligible for inclusion women had to be 18 years or older, have adequate access and ability to use the internet and a mobile phone as well as an adequate ability to speak, read and write Swedish. Women also had to meet diagnostic criteria for major depression according to a Structured Clinical Interview for DSM Axis I Disorders (SCID-I; First and Gibbon, 2004). Women had to have a screening score on the Montgomery-Åsberg Depression Rating Scale- Self report version (MADRS-S; Montgomery and Asberg, 1979; Svanborg and Asberg, 1994, 2001) between 15 and 35. Only women with no or a low risk of suicide as indicated by a score of 4 ("I often think that I'd be better off dead, and though I do not really want it, sometimes suicide feels like a possible way out") or less on item 9 on MADRS-S and the clinician's assessment during the semi-structured telephone interview were included. Current antidepressant medication was allowed if the treatment and dose had been stable for at least three weeks.

To minimise dropout due to miscarriages and to ensure that treatment was given during pregnancy, and not after, women had to be at least 10 and no more than 28 weeks pregnant. To ensure that participation in the current study was considered as an add-on and not as an alternative to maternity care, participants had to provide information on listing at a maternity clinic and were informed to attend regularly.

2.3. Exclusion criteria

Women scoring 5 or 6 ("I am actually convinced that my only way out is to die, and I think a lot about how to best go about killing myself") on MADRS-S item 9 at screening were excluded after a risk assessment and referral to adequate level of care. Ongoing psychological treatments that could potentially interfere with the current treatment led to exclusion. As did any current psychiatric or medical condition that was deemed as a significant contraindication for participation (for example psychosis or advanced cancer) or expected to be adversely affected by participation.

Also, participants who had a markedly high risk of terminated pregnancy (for any reason) or severe pregnancy related complications (for example preeclampsia) were excluded from participation.

2.4. Procedure

Women interested in participation logged on via the Internet Psychiatry Clinic's website (www.internetpsykiatri.se), filled out an informed consent e-form and completed an online questionnaire. Women eligible after screening were contacted for a semi-structured telephone interview that primarily consisted of the depression segment of the SCID-I interview and everything but the depression segment from the M.I.N.I. interview (version 6; Sheehan et al., 1998) to cover potential co-morbidities. Regular supervision with psychologists, obstetricians and psychiatrist were held to decide on all cases.

Eligible women were asked to log on and fill out an online questionnaire pre-measurement after which they were randomised to either treatment as usual (TAU) defined as a continuation of their current maternity care for 10 weeks, followed by optional ICBT, or to be given ICBT immediately as an add-on to maternity care. Post-measurement was performed 10 weeks later both online and with a telephone interview. The interviewer was not the woman's own therapist but was otherwise not blinded concerning treatment allocation. Fig. 1 shows the CONSORT-flow-chart for participants.

For ethical reasons participants in TAU were offered the ICBT, with therapist support, after they had completed post-measurements. Those who after their 10-week TAU-period had passed gestational week 28 were offered the ICBT starting 3–6 weeks postpartum instead.

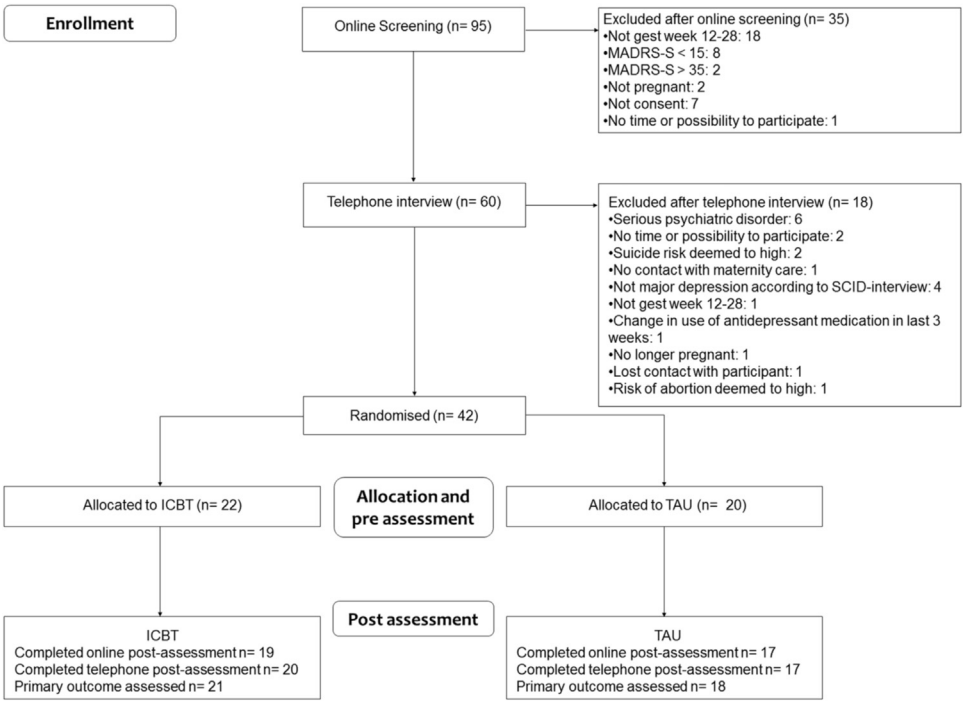

Fig. 1. CONSORT-flow chart of participants. Notes: ICBT = Internet based Cognitive Behavior Therapy, TAU = Treatment As Usual, MADRS-S = Montgomery-Åsberg Depression Rating Scale- Self report, SCID = Structured Clinical Interview for DSM Disorders.

2.5. Allocation

Randomisation was done in blocks of at least two included participants at a time. Lists of participant-codes were randomly ordered using list-randomisation (random.org). The first half of the list was allocated to ICBT. Randomisation was carried out by people outside of the study group.

2.6. Measures

2.6.1. Primary outcome

The primary outcome measure in this study was the Montgomery-Åsberg Depression Rating Scale Self-report version (MADRS-S) which is a widely used and validated scale for measuring depression that is especially designed to be sensitive to change (Montgomery and Asberg, 1979; Svanborg and Asberg, 1994, 2001). Scores range from 0 to 54 points with 13–19 points indicating mild depression, 20–34 points indicating moderate depression and 35–54 points indicating severe depression. MADRS-S was administered pre-, and post-treatment as well as weekly to monitor deterioration and suicidality and make last-observation-carried-forward sensitivity-analyses more accurate. To minimise missing data at post-measurement, MADRS-S was also part of the post-treatment telephone interview.

Remission was defined as having a post-score below 13 points on MADRS-S since that is a common cut-off for clinically significant depression on MADRS-S (Hedman et al., 2014).

Being a responder was defined as having achieved a reliable change towards the better. Reliable Change Index (RCI) was calculated using the formula $1.96*(SD1*\sqrt{2}*\sqrt{(1-rel)})$ (Wise, 2004) where $SD1$ is the initial standard deviation for the sample and rel is the test-retest reliability of the measure (MADRS-S test-retest reliability is 0.78 (Fantino and Moore, 2009)). This yielded a RCI of 8 points on the MADRS-S.

Negative effects related to treatment were also measured, in two of the ways suggested by Rozental et al. (2014): by measuring deterioration and by asking a simple open-ended question about adverse events post-treatment. To avoid underestimation of deterioration effects the Reliable Change criterion for negative change was set to 0.84 times the standard error of measurement instead of 1.96 in accordance to Wise (2004) meaning even a minimal deterioration would be identified. This yielded a cut-off for deterioration on MADRS-S of 4 points.

2.7. Secondary outcomes

Diagnosis of major depression after treatment was assessed the same way as before treatment, with the depression module of SCID-I semi-structured diagnostic interview (Spitzer et al., 1992).

To compare our sample with other samples of perinatal women, the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987; Bergink et al., 2011) was also administered. Scores range from 0 to 30 with 13 or more points being the cut off for depression during pregnancy. This scale is validated for Swedish pregnant women (Rubertsson et al., 2011) and often used for screening for perinatal depression. The General Anxiety Disorder 7-item scale (GAD-7) was used as a measure of anxiety (Spitzer et al., 2006). Scores range from 0 to 21 points with 10 points and above indicating clinical levels (Spitzer et al., 2006). The Insomnia Severity Index (ISI; Morin et al., 2011) was used to measure sleep problems. Scores range from 0 to 28, with 10 or above indicating clinical sleep problems. The EQ-5D-3L is a widely used general measure of health and function, that will be presented in the single weighted index score-form in this paper (Rabin and de Charro, 2001).

The Work and Social Adjustment Scale (WSAS; Mundt et al., 2002) measures levels of impairment caused by a condition. Scores range from 0 to 40 with scores below 10 points indicating sub clinical impairment and scores above 20 indicating moderately severe impairment or worse. In this study we administered two versions of this questionnaire, one asking about impairment caused by depression and the other about impairment due to pregnancy.

The Client Satisfaction Questionnaire-8 item version (CSQ-8; Attkisson and Zwick, 1982) measures satisfaction with treatment with scores from 8 to 32 and was used with the cut-offs described by Smith et al. (2014) where 8–13 indicates poor, 14–19 fair, 20–25 good and 26–32 excellent satisfaction.

2.8. Other measures

The Treatment Credibility Scale is a version of the credibility/expectancy questionnaire (Devilly and Borkovec, 2000) containing the items 1–4 and then an additional item on how well the respondent

thinks the treatment would work for similar problems. Scores range from 5 to 50.

Patients were asked post treatment if they believed that the fact that examples and cases were pregnancy-adapted and the treatment contained specific pregnancy-related material was a) important or necessary, and b) helpful, on two five-step likert-scales ranging from “Not at all” to “Very much so”.

Adherence and utilization was assessed via time spent logged on to the treatment platform, number of logins, messages sent to the therapist and also, the number of modules accessed and completed. In this treatment, patients completing six out of ten modules were considered completers since the first six modules contained the main components of CBT for depression i.e. behavioral activation and cognitive restructuring. This definition is the same used by Hedman et al. for the established ICBT treatment that the current ICBT is adapted from Hedman et al. (2014). We also measured time spent by therapists.

Patients were asked extensive questions about other treatments, both psychological and pharmacological at inclusion and after treatment to account for effects not due to the study itself.

The Alcohol-Use Disorders Identification Test (AUDIT; Saunders et al., 1993) and the Drug-Use Disorders Identification Test (DUDIT) are validated screening tools of alcohol or drug use respectively (Bergman and Kallmen, 2002; Berman et al., 2005). Scores range from 0 to 40 on both scales. For women, 6 or more points on the AUDIT indicate abuse, and anything other than 0 points is a risk indicator on DUDIT (Berman et al., 2005).

2.9. Intervention

We defined ICBT as it is described in Andersson et al. (2005) as guided self-help via the internet. The intervention consisted of an adapted version of the ICBT for depression currently in use in regular care at the Internet Psychiatry Clinic in Stockholm since 2007 (Hedman et al., 2014). The treatment was a guided self-help treatment where reading material (about 75,000 words), assessments, homework and work-sheets were delivered via a secure online platform. Patients also had a CBT-trained, and regularly supervised, therapist providing regular feedback, encouragements and support in written messages mirroring the interventions described in Andersson et al. (2005).

Adaptations consisted of an extended description of depression and its relation to pregnancy. For instance, explaining that it could be caused, or exacerbated, by biological or psychosocial consequences. It also underscores that pregnancy can be completely unrelated to the depression, but still be a very relevant part of your situation. Specific information about how pregnancy could be causing or maintaining depression due to feeling unwell, changing habits, and having new relational or practical problems to solve etcetera was added as a second module. Focus here was on sense making and de-stigmatization, and the contrast between societal norms and social expectations about how one ‘should’ feel and think when pregnant as opposed to how many feel. A module on relationships was also added, since issues with close personal relationships and role transitions often occur. The rest of the treatment was essentially the same as Hedman et al. (2014), and Andersson et al. (2005) but with most examples and case stories changed to be about pregnant or child rearing women.Table 1 shows an outline of the treatment content. Modules labelled “Extra” were given in the order deemed most suitable based on patient preferences and the clinicians’ judgement. This was decided during the last of the fixed-order modules. We called them Extra to underscore that these modules are not as essential and to minimise the feeling of being behind schedule for slower patients.

2.10. Statistical analyses

IBM SPSS 22 was used for all analyses. For continuous variables, after checking for normality and assumptions, between group differences were tested with ANCOVAs with pre-treatment measures as covariates and within group differences before and after treatment were instead tested with paired *t*-tests. To account for the small sample size Hedges’ *g* was used as the effect size. Categorical data was analysed with 2-sided Fisher's exact tests, and relative risk (RR) was used as the effect size.

All analyses were done in line with the intent to treat principle. Missing MADRS-S scores post treatment were imputed from telephone-administered MADRS-S when possible using the regression coefficients from Hedman et al. (2013). This was done for three patients, two in ICBT and one in TAU. Since attrition was low, no other data was imputed or replaced for the main analyses. As a sensitivity analysis, missing data was replaced according to last observation carried forward to see if these results differed.

3. Results

3.1. Baseline characteristics

Baseline characteristics are presented in Table 2. More women randomised to TAU had ever had an abortion (Fisher's exact p = 0.049). This was the only significant difference between ICBT or TAU at baseline.

3.2. Treatment adherence and utilization

On average, patients logged on to the platform 34.1 times during their 10-week treatment (sd = 15.7) and sent 14.1 messages to their therapist (sd = 7.8). They completed on average 5.3 modules (sd = 2.5) but were given on average 7 (sd = 2.1) out of a possible 10 modules. The proportions of patients completing modules 1 through 10 were 96%, 96%, 86%, 77%, 59%, 46%, 23%, 9%, 18%, and 18% respectively. Eighty-two percent of patients received six or more modules. Therapist spent on average a total of 2 h and 30 min (sd = 1 h and 50 min, range 35 min to 6,5 h) per patient over the course of the 10 weeks.

3.3. Treatment credibility and satisfaction

Treatment Credibility Scale (TCS) mean score was 33.8 (sd = 9.1) two weeks into treatment. Client Satisfaction Questionnaire (CSQ) mean score was 23.8 (sd = 3.1), indicating good satisfaction according to Smith et al. (2014) where 8–13 indicates poor, 14–19 fair, 20–25 good and 26–32 excellent satisfaction. All but one patient believed that the pregnancy-adaptation of the treatment were important and helpful, and she simply stated that she did not think it made any difference.

3.4. Primary outcome – depressive symptoms

As presented in Table 3, the ICBT group had significantly lower depression scores post treatment compared to TAU ($p < 0.001$) and the between groups effect was large (Hedges’ $g = 1.21$).

Remission (i.e. MADRS-S score < 13) was observed in seven patients (33%) in ICBT and two patients (11%) in TAU. This was not statistically significant between groups, largely since few patients altogether had a post-score under 13.

Responder status (i.e. change of 8 points or more towards the better on the MADRS-S) was achieved by 71% of ICBT-patients as compared to 22% in TAU. This difference was statistically significant (n = 39, Fischer's exact p = 0.004) and large, with an RR of 0.36 (95% CI = 0.16–0.82).

3.5. Secondary outcomes

All secondary outcomes are summarised in Table 3. Both groups had, within themselves, significantly lower post treatment scores on the

Table 1
Treatment contents.

Block	Module	Main components	Homework
Introduction	1	Psychoeducation about depression, antenatal depression, CBT and the treatment platform	Goal setting and values
Being pregnant	2	Information about myths, facts and the in-between concerning pregnancy related physiological and cognitive changes, views and stigma around antenatal depression	Making a social network inventory (From whom can you get help with what?)
Behavioral activation	3	Psychoeducation and rationale (i.e.how to conceptualise depression from a CBT perspective and why and how the suggested methods might work). Focus is on positively reinforced behaviors	Baseline registration of positive/negative activities in a calendar, list potentially reinforcing behaviors to try out or increase
	4	More behavioral activation, focusing on negatively reinforced behaviors, avoidant behaviors and procrastination	Goal-setting and strategies for increasing the reward of important but tasking/boring activities
Cognitive restructuring	5	Psychoeducation about negative automatic thoughts and acceptance	Listing your typical negative automatic thoughts and during the week observing and writing down your Negative Automatic Thoughts as they happen
	6	Working with negative automatic thought. Cognitive biases and traps, assumptions and how to challenge them. Problem solving	Revisiting goals and values, finding your negative assumptions and alternative thoughts
Relationships	Extra	Psychoeducation about relationships, communication, role transitions for families	Your parents' relationship, pros/cons of the role "mum", which relationships increase/lower your mood, try a communication strategy
Anxiety and worry	Extra	Psychoeducation about anxiety in general and fear of labor	Reflection about fear of labor/delivery, problem solving, worry-time, worst case scenarios
Sleep problems	Extra	Psychoeducation about sleep and sleep during pregnancy	Sleep hygiene, sleep diary, sleep restriction
Summary and relapse prevention	10	Summary and relapse prevention	Summarise and plan for setbacks, mindfulness exercise

EPDS and the WSAS-depression version. ICBT had significantly lower within group scores on the GAD-7, while between groups comparison showed no significance. Differences on the ISI, WSAS-Pregnancy version and the EQ-5D were non-significant both within group and between groups. Sensitivity analyses with last observation carried forward did not change the results of any statistical analyses.

The depression module of the SCID-I interviews at post treatment showed a large and significant difference between the groups (n = 36, Fischer's exact p = 0.002, RR = 0.42 [95% CI = 0.23–0.77]). Sixty-three% of patients in ICBT no longer met diagnostic criteria for depression compared to 12% in TAU.

3.6. Negative effects

Two patients reported one minor adverse event, which was that they felt stressed about not keeping up with the treatment program. Some other patients reported this experience spontaneously in response to other questions but not when asked specifically about negative effects.

Deterioration (i.e. 4 points or more increase on the MADRS-S) was observed in three participants in TAU and one participant in ICBT but the difference was not significant. The three patients in TAU who deteriorated all had pre-treatment scores above 20 and deteriorated between four to six points to post treatment. The ICBT-patient that deteriorated however, had a pre-treatment MADRS-S score of 8 points after a large reduction from screening, and deteriorated up to 13 points at post treatment.

3.7. Other treatments

At inclusion one woman in each arm was taking antidepressant medication. The only change to post-treatment was that the woman in ICBT lowered her dose of sertraline from 150 mg/day to 100 mg/day. Five women in ICBT and two in TAU were taking levothyroxine at intake. After treatment, only two in each arm used levothyroxine. Similarly, at intake three women in ICBT and one in TAU were taking promethazine and this decreased to one in each arm post treatment. No differences were significant.

Eight women in each arm had initiated some form of counselling or psychological treatment outside the study during the treatment period. Most common were counselling sessions at the maternity clinic or at specialised centres for fear of delivery.

4. Discussion

4.1. Main findings

The major novel findings of this clinical trial are that adding ICBT adapted for antenatal depression to usual maternal care was acceptable and more effective in reducing depressive symptoms than treatment as usual alone.

Between group effects were large, even though depressive symptoms decreased significantly also in the control group. This decrease in the control group might reflect spontaneous remission, or can be due to less negative effects of pregnancy symptoms over time. The latter is contradicted by the finding that perceived every-day disability due to pregnancy did not change during treatment. More probable reasons are regression to the mean or that regular maternal care did have some positive effects on depression. There were also eight women in TAU who initiated some form of counselling during the study. While the treatment effect was substantial many women in ICBT were still above cut-off levels for clinically significant depressive symptoms post-treatment both on the MADRS-S and the EPDS. However, the proportion of women meeting criteria for depression when reassessed with the depression module of the SCID interview was lower in ICBT compared to TAU. That assessment was however not blind concerning allocation and may be biased.

The main outcome for depression, measured with MADRS-S, which is specifically designed to measure change in depression (Svanborg and Asberg, 1994, 2001), was clearly significant. However, the screening tool EPDS did not present any significant group differences. This indicates that even though EPDS is well validated as a screening tool (Rubertsson et al., 2011) and has been used as an outcome in postpartum depression trials (O'Mahen et al., 2014; Pugh et al., 2016), it might be less suitable as an outcome measure in either the context of antenatal depression or perhaps in samples with high levels of depression. Anxiety could also be a confounder behind this discrepancy. The EPDS has been found to be two-dimensional and measure anxiety to the same extent as it measures depression (Brouwers et al., 2001). The treatment in the current trial did not focus on anxiety and did not lower those symptoms to the same extent.

Levels of anxiety decreased significantly in the ICBT group, but between group effects were not statistically significant which was likely due to baseline scores on anxiety not being very high combined with the fact that the ICBT focused on depression leading to lower effects on

Table 2
Baseline sociodemographic and psychosocial characteristics.

		ICBT (n = 22)	TAU (n = 20)
Age (mean(SD))		31.2 (3.7)	30.8 (5.3)
In a committed relationship		96%	100%
With children		50%	55%
Gestational week at screening (mean(SD))		15.9 (6.5)	18.6 (6.5)
First pregnancy		46%	25%
Miscarriage ever		27%	40%
Abortion ever		18%	50%
Preeclampsia ever		0%	15%
Highest education:	High school	14%	40%
	University	86%	60%
Employment status:	Working or self employed	82%	75%
	Sick-leave	9%	25%
	Unemployed	5%	5%
	Maternity leave	14%	10%
Previous episodes of depression		96%	85%
Previous episodes of AND		27%	40%
Previous episodes of PND		27%	35%
Comorbidities at intake:	GAD	32%	30%
	Panic Disorder	27%	25%
	Agoraphobia	9%	35%
	Social Anxiety Disorder	23%	25%
	OCD	0%	5%
	PTSD	5%	15%
	Bulimia	5%	0%
	Alcohol Abuse (last 12 months)	5%	5%
	Alcohol dependency (last 12 months)	5%	5%
AUDIT score (mean(SD))		2.8 (3.1)	3.2 (4.6)
DUDIT score (mean(SD))		0.3 (0.8)	0.2 (0.9)
Previous psychological treatments:	No previous psychological treatments	14%	20%
	Previous CBT	46%	40%
	Previous PDT	27%	15%
	Previous IPT or RPT	9%	0%
	Previous counselling	46%	50%
Ongoing psychological treatments:	No ongoing psychological treatments	68%	60%
	Ongoing Counselling or low intensity psychological treatment	37%	35%
Antidepressant medication:	Previous use	55%	70%
	Previous use during pregnancy or breastfeeding	18%	15%
	Ongoing use	5%	5%

Notes: ICBT = Internet based Cognitive Behavior Therapy, TAU = Treatment As Usual, SD = Standard Deviation, AND = Antenatal depression, PND = Postnatal depression, GAD = Generalized Anxiety Disorder, OCD = Obsessive Compulsive Disorder, PTSD = Post Traumatic Stress Disorder, AUDIT = Alcohol use disorder test, DUDIT = Drug use disorder test, CBT = Cognitive behavior therapy, IPT = Interpersonal psychotherapy, PDT = Psychodynamic therapy, RPT = Relational psychotherapy.

anxiety not possible to confirm with the current statistical power. It is possible that a tailored (Hallgren et al., 2015) approach would have had a larger effect on anxiety especially if it was able to target previous pregnancy trauma (PTSD; Nieminen et al., 2016b) or fear of childbirth (a specific phobia; Nieminen et al., 2016a). Insomnia severity showed little or no change over time for any group. This is not very surprising considering the low levels of symptoms at intake. Also, sleep related treatment components, as with anxiety, consisted of only one module each, which was positioned late in the treatment and not given to everyone.

Measures of general health, disease burden and everyday function (EQ-5D and WSAS) were relatively static over time, one exception being that both groups perceived a slight decrease in burden of depression. These results may be confounded by symptoms of ongoing pregnancy and should be interpreted cautiously.

The current treatment was as utilised and efficacious as other similar ICBT-treatments for depression (Hedman et al., 2014). Almost all patients believed that the pregnancy-adaptations were important and helpful. Importantly, no patient reported feeling offended or said that examples were stereotypical or simplistic. This is an important aspect of the acceptability of this treatment protocol as more specialised and specific examples potentially increase the risk of causing offence if those adaptations are not perceived as accurate.

4.2. Strengths

The ICBT format is highly structured and controlled which increases treatment fidelity compared to traditional CBT, where therapists can more easily deviate from the manual with or without even noticing, so called therapist drift. Also, the therapists had basic CBT training but no prior experience nor any special education or training in order to treat this specific population, demonstrating one strength of this kind of specialised treatment manual. The proof of concept would have been diminished had the therapists been experts in perinatal mental health.

Another important strength is the low levels of attrition post-treatment which means that we can be relatively confident in our main findings.

4.3. Limitations

The number of included patients was small, which increases the risk for inflated effect sizes, and gives less power to detect small differences. Also, long term follow-ups are missing and, with that, any possible effects this kind of intervention might have on post-partum depression. These limitations call for future replications and extensions of the current design. Also, the patients in the current study were self-referred. This makes generalization to a clinical setting using other ways for recruitment somewhat problematic. However, even in settings providing ICBT in regular care, the main part of the patients can come from self-referral (El Alaoui et al., 2015; Hedman et al., 2014).

The diagnostic assessment of depression post treatment was not done by blind assessors, and thus may be biased, and therefore less reliable than the primary outcome, which was a self-report scale. However, the diagnostic assessment was done with a structured interview and most cases were decided on together with a supervisor, who was kept blind until a decision had been made.

4.4. Interpretation (in light of other evidence)

The effects on antenatal depression are highly comparable to those found for ICBT-programs as well as traditional CBT for depression (Hedman et al., 2012; Hofmann et al., 2012; Cuijpers et al., 2013). The Internet Psychiatry Clinic's regular depression treatment within group effect size was 1.27 (95% CI = 1.14–1.39) (Hedman et al., 2014) and in this study the within group effect was 2.10 (95% CI = 1.12–3.10) both of which are large and also overlap. This is a positive indication that our adaption to antenatal depression was successful, and that this group is treatable with internet-based CBT.

These positive results are not likely due to our sample having less severe or less chronic symptoms than the population, since 90% reported previous episodes of depression and there were high levels of comorbidities. Considering that the perinatal period is a common time for a first episode of depression (Becker et al., 2016), our sample might even be slightly more chronic than usual.

Treatment credibility was high and similar to credibility ratings in similar ICBT studies (Carlbring et al., 2003; El Alaoui et al., 2015). Client satisfaction was good and closely mirrors the satisfaction scores obtained at the Internet Psychiatry Clinic's regular depression treatment (Hedman et al., 2014). Also, data on utilization (i.e. messages sent, time

Table 3
Outcomes based on observed data.

	Group	Pre	Post	Within group effect size (Hedges *g* (95% CI))[a]	Between group statistics (ANCOVA)	Between group effect size (Hedges *g* (95% CI))
MADRS-S	ICBT	24.2 (5.2)	14.3 (4.6)	2.11 (1.12–3.10)**	F = 15.31, p < 0.001**	1.21 (0.50–2.92)
	TAU	24.4 (5.9)	21.1 (6.4)	0.68 (−0.20–1.56)*		
EPDS	ICBT	16.3 (3.9)	12.4 (4.9)	0.89 (0.02–1.77)**	F = 1.06, p = 0.31	0.52 (−1,08–2.12)
	TAU	18.5 (4.5)	15.0 (4.9)	0.73 (−0.18–1.64)*		
GAD−7	ICBT	11.6 (4.5)	7.2 (4.1)	0.93 (0.05–1.81)**	F = 2.81, p = 0.10	0.63 (−0.84–2.10)
	TAU	13.1 (5.7)	10.1 (5.3)	0.42 (−0.47–1.31)		
ISI	ICBT	12.9 (4.8)	11.9 (5.7)	0.21 (−0.63–1.05)	F = 1.94, p = 0.17	0.44 (−1.25–2.12)
	TAU	12.5 (4.7)	14.2 (4.5)	−0.20 (−1,09–0.68)		
WSAS-Pregnancy	ICBT	18.4 (10.2)	19.6 (9.7)	−0.10 (−0.94–0.73)	F = 0.15, p = 0.70	−0.03 (−3.18–3.12)
	TAU	13.7 (12.3)	19.3 (9.6)	−0.40 (−1.30–0.49)		
WSAS-Depression	ICBT	23.9 (7.6)	18.9 (9.6)	0.51 (−0.34–1.36)*	F = 0.61, p = 0.44	0.49 (−2.27–3.24)
	TAU	29.3 (7.0)	23.1 (6.9)	0.92 (−0.01–1.85)*		
EQ−5D	ICBT	0.4 (0.3)	0.4 (0.4)	−0,04(−0,87–0,80)	F = 0.07, p = 0.80	0.08 (−0.03–0.20)
	TAU	0.4 (0.4)	0.4 (0.3)	0,03 (−0,86–0,91)		

Notes: ICBT = Internet based Cognitive Behavior Therapy, TAU = Treatment As Usual, MADRS-S = Montgomery-Åsberg Depression Rating Scale- Self report, EPDS = Edinburg Postnatal Depression Scale, GAD-7 = Generalized Anxiety Disorder 7-item Scale, ISI = Insomnia Severity Index, WSAS = Work and Social Adjustment Scale- depression/pregnancy version, EQ-5D = EuroQol 5 Dimensions scale index.

** difference is significant p < 0.01.

* difference is significant p < 0.05.

[a] comparison made with paired *t*-test.

spent logged in, and therapist time) in this study are almost identical to that found at the Internet Psychiatry Clinic (Hedman et al., 2014) with the exception of completed modules where the current study had slightly lower levels of module completion. That might however be explained by the regular ICBT-program being available for patients during 12 weeks rather than 10 (Hedman et al., 2014).

Also, deterioration was very low. Rozental and colleagues shows that ICBT has the same rates of deterioration as other treatments, normally 5–10% of patients (Rozental et al., 2015), meaning that this treatment is at least as, if not more, safe as other non-pharmacological options.

One potential problem with specialized treatments is that therapists may fail to keep to the many protocols, thereby decreasing fidelity (McHugh et al., 2009) or hinder dissemination. In the current study however, changes were mostly limited to examples and case-stories, while the interventions are the same as in general ICBT for depression. In this trial, the supervisor was experienced in ICBT and depression, but not perinatal mental health and none of the therapists had worked with perinatal mental health before. ICBT protocols that are adapted in this manner have a development cost but the costs for dissemination should theoretically be low.

Whether the adaptations made to this treatment protocol were indeed necessary to achieve this effect or these levels of adherence is unknown, but can be tested in a future RCT comparing a specialized ICBT protocol to a general one. However, it is possible that the existence of treatments that are explicitly for perinatal mental health increase the likelihood of women seeking out or being referred to treatment, decreasing the number of women suffering in silence. It can also modify expectations when going into treatment, which could affect outcomes. ICBT has the potential for specific tailoring to both symptomatology and different demographic sub-groups with the click of a button once various versions of rational and example texts exist. Further studies are needed to explore this potential.

5. Conclusion

This is to our knowledge the first RCT of ICBT for antenatal depression. The study shows that this is an acceptable, safe, and efficacious alternative even with a heavily burdened sample, though many women will not be completely symptom free after treatment.

From a general clinical perspective, this study confirms that traditional CBT interventions can be offered to women suffering from antenatal depression and that adaptations can be limited to rationale, psychoeducation, and what examples are used, rather than inventing a new set of interventions. The findings also serve as a proof of concept for the possibility to customize an existing, general ICBT-program for specific subgroups.

The most common reason for exclusion in this study was being too far gone in gestation. In clinical practice however, there might not be a strong reason to wait until after delivery rather than initiate treatment that would still be ongoing by the woman's due-date. That exclusion criterion was mainly for minimizing attrition.

These findings still need to be replicated in other settings and long term outcomes for mother and child need to be assessed. Future research is also warranted to determine how to best reach women suffering from antenatal depression, perhaps as their first episode of depression, and who do not have a history of mental illness and seeking care.

Disclosure of interests

The authors have no conflicts of interest.

Details of ethics approval

This study was approved by the Regional board of research ethics (Etikprövningsnämnden) in Stockholm (EPN) as protocol DNR 2014/1959-31/1. The study was registered as a clinical trial before recruitment began. The ClinicalTrials.gov Identifier for the study is NCT02366429.

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Contribution of authorship

EF designed the ICBT-program together with VK, and took part in the design of the study, applied for ethical approval, treated patients, coded, analysed and interpreted the data, and wrote the first draft of the paper;

MB and MBW provided comments on treatment contents, and supervised clinical assessments pertaining to perinatal mental health and provided critical comments on the paper;

FH was the main clinical supervisor during the treatment phase, and also provided critical comments on the treatment contents and the paper;

JN and BSvS provided comments on treatment contents, and supervised clinical assessments pertaining to obstetrics and gynecology and provided critical comments on the paper;

SK, ES, CE and JLvdL contributed to treatment contents, worked extensively with recruitment, assessed, treated patients, collected and coded data, and provided critical comments on the paper;

JJ took part in the design of the study and also provided critical comments on the paper;

KW is principal investigator of the larger MAGDALENA-trial of which this study is a part and she took part in the design of the study and provided critical comments on the paper;

VK, principal investigator of this study and main supervisor of EF, supervised and took part in designing the ICBT-program, designing the study and applying for ethical approval as well as data analysis and writing the first draft.

Conflicts of interest

None.

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