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Effects of psychological treatment of mental health problems in pregnant women to protect their offspring: randomised controlled trial

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Background

Perinatal depression and anxiety are associated with unfavourable child outcomes.

Aims

To assess among women with antenatal depression or anxiety the effectiveness of prenatally initiated cognitive–behavioural therapy (CBT) on mother and child compared with care as usual (CAU). Trial registration: Netherlands Trial Register number NTR2242.

Method

Pregnant women ($n = 282$) who screened positive for symptoms of depression and/or anxiety were randomised to either CBT ($n = 140$) or CAU ($n = 142$). The primary outcome was child behavioural and emotional problems at age 18 months, assessed using the Child Behavior Checklist (CBCL). Secondary outcomes were maternal symptoms during and up to 18 months after pregnancy, neonatal outcomes, mother–infant bonding and child cognitive and motor development at age 18 months.

Results

In total, 94 (67%) women in the CBT group and 98 (69%) in the CAU group completed the study. The mean CBCL Total Problems score was non-significantly higher in the CBT group than in the CAU group (mean difference: 1.38 (95% CI −1.82 to 4.57); $t = 0.85$, $P = 0.399$). No effects on secondary outcomes were observed except for depression and anxiety, which were higher in the CBT group than in the CAU group at mid-pregnancy. A *post hoc* analysis of the 98 women with anxiety disorders showed lower infant gestational age at delivery in the CBT than in the CAU group.

Conclusions

Prenatally initiated CBT did not improve maternal symptoms or child outcomes among non-help-seeking women with antenatal depression or anxiety. Our findings are not in line with present recommendations for universal screening and treatment for antenatal depression or anxiety, and future work may include the relevance of baseline help-seeking.

Declaration of interest

B.W.M. reports consultancy for ObsEva, Merck, Merck KGaA and Guerbet.

Keywords

Cognitive behavioural therapy; anxiety; depression; pregnancy; child development.

Perinatal mental ill health is common around the world.[1] It is associated with unfavourable neonatal outcomes, such as low birth weight, and disadvantages in several domains of child development and psychosocial problems in adolescence, including depression.[2] In turn, these negative outcomes link to subsequent decreased mental and cardiovascular health in adulthood.[3] Improving perinatal mental health could therefore have enormous global health relevance. This insight has sparked the interest in perinatal mental health as an important target for prenatal interventions, even though detailed knowledge of the mechanisms involved is lacking.[2] Because the safety of antidepressant medication during pregnancy is debated, most research has been directed at the effects of preventive or therapeutic psychological interventions, including cognitive–behavioural therapy (CBT).[4] A recent meta-analysis showed CBT during pregnancy and the first year postpartum to be effective in improving perinatal mental health, both in terms of treatment and illness prevention.[5] However, the included randomised controlled trials (RCTs) had considerable risk of bias, and only just over half of studies reported intention-to-treat analyses. Remarkably, only four RCTs on antenatally initiated CBT studied child outcomes.[6–9] However, three of these trials had small samples, and the fourth, the Thinking Healthy Programme RCT, did not include offspring behavioural problems.[6] Furthermore, while the scientific literature provides evidence for an effect of CBT in treating and preventing perinatal depression,[5] no such evidence exists for perinatal anxiety. Notwithstanding limited evidence, the guidelines of the American Psychiatric Association (APA) and the American College of Obstetricians and Gynecologists (ACOG),[10] and other current guidelines,[11] as well as a recently issued evidence report and systematic review,[12] suggest universal perinatal screening for depression and anxiety in all women and, if indicated, interventions such as CBT or other treatment. Therefore, the aim of the present RCT was to assess, among women from the general population who screened positive for moderate prenatal symptoms of depression or anxiety but were not seeking help for these, the effects of individual CBT compared with care as usual (CAU) on mother and child.

Method

Design and participants

The PRegnancy Outcomes after a Maternity Intervention for Stressful EmotionS (PROMISES) trial is a CONSORT-compliant parallel-group assessor-masked multicentre RCT with a published protocol.[13] The study was registered in The Netherlands Trial Register (trialregister.nl) as NTR2242. We recruited women in 109 midwifery practices and 9 obstetrics and gynaecology departments of hospitals in The Netherlands. All women during their booking visit at the collaborating practices between 10 and 12

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weeks of pregnancy, which is part of standard care, were screened for the purpose of the study. They were provided with study information, a consent form and two self-report questionnaires: the 6-item State–Trait Anxiety Inventory (STAI) and the 10-item Edinburgh Postnatal Depression Scale (EPDS) to assess symptoms of anxiety and depression respectively.[14,15] Women with at least moderate anxiety or depression, defined as a score of 42 or higher on the STAI or 12 or higher on the EPDS, were eligible. Women were excluded if they had substantial physical disease, had a multiple pregnancy, showed a high suicide risk on the MINI-International Neuropsychiatric Interview,[16] had a history of bipolar disorder, psychoses or manic disorder, had misused substances, were receiving psychotherapy or did not speak Dutch.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human participants were approved by the medical ethics committee of the University Medical Centre Groningen (2009.235). Written informed consent was obtained from all participants.

After enrolment by an independent collaborator we recorded (at around 14 weeks' gestation) baseline age, parity (nulliparous/multiparous), marital status (single or otherwise), socioeconomic status (SES) and smoking status (yes/no). Indicators of SES were family annual gross income and educational levels of the participant and her partner. Educational level was defined as the highest completed education, divided into three categories: low (elementary and lower levels of secondary education), intermediate (higher levels of secondary education and intermediate vocational education) and high (higher vocational education and university). Family annual gross income was divided into low (€0–€30 999), moderate (€31 000–€59 999) and high (€60 000 or more). For analyses these indicators were equally weighted and categorised into low, middle and high SES tertiles.[17] Anxiety disorder, post-traumatic stress disorder (PTSD) and depressive or comorbid (anxiety and depression or PTSD and depression) disorders were diagnosed at baseline using the Structured Clinical Interview for DSM-IV (SCID-II).[18]

Randomisation and masking

Eligible women were randomised 1:1 to either CBT or CAU by an independent assistant after baseline assessments using a computer-generated list created by a central service before the study began, to guarantee that the allocation sequence was concealed. We stratified for parity (nulliparous/multiparous) and the three categories of SES, and used randomly permuted blocks of random sizes varying between two and eight. Outcome assessors were masked to treatment allocation during the study.

Interventions

Licensed psychologists ($n = 31$) with at least 2 years' postdoctoral training including CBT and CBT supervision provided the CBT. They received for the study an additional 2 days of training on antenatal CBT (for depression, anxiety disorders and PTSD) and supervision during. The treatment protocol consisted of 10–14 individual sessions, of which 6–10 were intended to be delivered during pregnancy. Sessions were scheduled from 20 weeks' gestation up to 3 months postpartum; the exact timing of the sessions was planned on the basis of shared decision-making with the participant. The treatment encompassed several optional modules, with evidence-based CBT interventions focusing on the treatment of anxiety disorders (exposure, response prevention and cognitive-challenging work), depressive disorders (additional behavioural activation), or trauma and PTSD (exposure, imagery and rescripting). In addition, the overall focus was on identifying and changing dysfunctional cognitions and beliefs. Each session also addressed pregnancy-related cognitions and attitudes, and selected evidence-based CBT interventions for specific anxiety and depressive disorders and PTSD were offered. All sessions were structured, explaining the rationale and giving and discussing homework assignments. A treatment manual is available on request. Regular therapist supervision was given by C.L.H.B.. Allocation of participants to CBT therapists was performed by an independent collaborator on the basis of location and availability. Participants assigned to CAU were advised to contact their general practitioner (GP) or midwife. In line with the pragmatic nature of the trial, no restrictions were imposed on additional treatments in either group. All such additional treatment was assessed.

Outcomes

The primary outcome was the total of behavioural and developmental problems in the child at 18 months of age, assessed using the validated parent-reported Child Behavior Checklist for Ages 1.5–5 (CBCL/1.5–5), including the Caregiver-Teacher Report Form (C-TRF),[19] substituting non-parental caregivers for teachers in our preschool sample and averaged with the parent's report. The CBCL contains 99 items rated on a three-point scale: 0 (not true), 1 (somewhat or sometimes true) and 2 (very true or often true), and provides ratings of seven syndrome scales. We analysed total scores (range: 0–198) and the internalising (0–72) and externalising subscales (0–48). Higher scores indicate greater severity. Secondary outcomes were maternal anxiety and depression during pregnancy and postpartum, mother–infant bonding, neonatal outcomes and child development.

Maternal anxiety and depression were assessed at 24 and 36 weeks' gestation and at 6 weeks and 3, 6, 12 and 18 months postpartum using the STAI and EPDS respectively. The Dutch version of the Postpartum Bonding Questionnaire (PBQ), administered between 6 and 18 months postpartum, was used to quantify the quality of mother–infant bonding.[20] This scale is composed of 25 statements that are to be rated on a six-point Likert scale ranging from 'always' (0) to 'never' (5). The sum of the 25 items forms the total PBQ scale (range 0–125), with higher scores reflecting a more problematic mother–infant bond. Midwives and gynaecologists generated standardised birth reports from which our neonatal outcomes were derived. They comprised birth weight, gestational age at delivery and Apgar scores at 1 and 5 min postpartum. When the children were approximately 18 months of age, cognitive, fine and gross motor development levels were assessed using the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III).[21] Assessments were performed in hospital or in the participant's home by trained research assistants and interobserver variance was limited by supervision after reviewing videotaped assessments. BSID-III outcomes were reported as composite scales with an age-dependent normed mean of 100 and a standard deviation of 15.

Sample size

Effect sizes (Cohen's d) $\geq$0.35 on the primary outcome (corresponding to >4 points on the CBCL) were considered relevant and in agreement with the effect size of approximately 0.4 for anxiety and depression treatment in the general population.[22] With an α of 5% and a power $(1 - \beta)$ of 80%, this effect size can be detected with 260 participants. To account for drop-out we aimed at 300 randomisations.

Statistical analysis

Analyses were primarily performed according to the intention-to-treat principle. Secondary analyses were planned as per protocol, i.e. restricted to those participants who attended a minimum of 10

sessions. Analyses included stratification variables as added independent variables. When baseline characteristics were not balanced between the randomised groups, they were adjusted for in additional analyses. We used linear mixed-effects models including a random intercept and random slope for each participant, with an unstructured covariance matrix to quantify treatment effects on maternal anxiety and depression level while accounting for their correlated values over time. Treatment effects were estimated by entering interaction terms of group × time as a categorical independent variable in order to obtain time-specific group differences. Remaining outcomes were analysed using linear regression models. We undertook protocol-defined subgroup analyses across the stratification variables. We further performed exploratory *post hoc* analyses according to the presence of a baseline anxiety disorder (including PTSD), depressive disorder or their comorbidity, and according to baseline severity, defined by symptom levels exceeding the EPDS (≥12) and STAI (≥42) thresholds, prior to inspection of the data. Differential treatment effects in subgroups were evaluated by testing the statistical significance of treatment × subgroup interaction terms. Subgroup-specific effects were reported only if the interaction was statistically significant. Effect parameters were supplied with test statistics, 95% confidence intervals and *P*-values.

The proportion of missing data ranged from 0 to 49% (last follow-up) for the maternal data and from 0 to 38% (BSID-III scores) for the child variables. Multiple imputation was used for incomplete data under the missing at random (MAR) or missing completely at random (MCAR) assumption.[23] The missing data mechanism was studied for each of the variables by predicting its missingness, for example because of loss to follow-up, from the other variables. This was done using multivariable logistic regression analyses. These analyses showed explained variances ranging from 4.2 to 12.3% (Nagelkerke's R^2), implying that data were at least partly missing at random and consequently multiple imputation may have minimised bias. The final imputation model included all variables used in the analyses, those that predicted missingness of a variable, for example because of attrition, or its value. Fifty data-sets were imputed and results were pooled using Rubin's rules. Analysis after multiple imputation is considered superior to complete case analysis.[23] Because neither MAR nor MCAR can be proved, we added complete case analyses as a sensitivity analysis. Statistical significance was set at 0.05, two-sided.

Results

Between 1 May 2011 and 1 September 2014 we screened 8143 pregnant women for symptoms of depression and/or anxiety. Of these, 1284 (16%) screened positive, 901 (70%) fulfilled inclusion criteria and 282 (31%) were randomised and included in the intention-to-treat analyses (Fig. 1). Of the total sample, 149 (53%) were screened and recruited in the hospital setting, with 71 randomised to CBT and 78 randomised to CAU. We terminated inclusion before reaching our target sample size of 300 solely for reasons of slow enrolment due to competing studies and high refusal rates.

We applied commonly used cut-off scores for the two screening instruments. On the EPDS, 50.0% of the screened women scored ≥10, 32.4% ≥12 and 22.4% ≥13 among the 282 included women; we included in the trial those who scored ≥12. On the STAI, we included the 86.9% of screened women who scored ≥42. The randomised groups (CBT $n = 140$; CAU $n = 142$) were comparable on most baseline variables, although anxiety, PTSD and depression as single disorders were more prevalent in the CBT group, and diagnosis of comorbid depression and an anxiety disorder or PTSD was more prevalent in the CAU group (Table 1). Anxiety disorders comprised generalised anxiety disorder or anxiety disorder not otherwise specified ($n = 64$; 22.9%), obsessive–compulsive disorder ($n = 25$; 8.9%), agoraphobia or panic disorder ($n = 23$; 8.2%), social phobia ($n = 54$; 19.3%) and specific phobia ($n = 24$; 8.6%), with no remarkable differences between randomised groups.

In the CBT group, 15 participants refused to continue with the intervention immediately after randomisation, expecting too high a burden. Participants who entered the intervention ($n = 125$; 89%) received an average of nine sessions (range 1–15) and 68 (49%) received ten or more sessions. Most sessions were delivered antenatally. Prior to the effectiveness analyses, we deemed this too small a proportion for per protocol analyses and therefore revised this criterion downward to having completed six or more sessions; this criterion was fulfilled by 93 participants (66%). Reasons for not completing treatment included no more symptoms ($n = 5$), practical or personal issues ($n = 9$), intervention too burdensome ($n = 9$), pregnancy-related complications ($n = 5$) or unknown ($n = 4$). Only four study participants used antidepressants, namely a selective serotonin reuptake inhibitor (SSRI), two in the CBT group and two in the CAU group. In each group, one participant was already taking an SSRI at baseline and another started after randomisation. Four other participants, two in each group, used low-dose benzodiazepines. In total 206 participants (73%; $n = 98$ in the CBT group, $n = 108$ in the CAU group) responded on the maternal symptom questionnaires at 36 weeks' gestation, of whom 140 (50% of the total sample; CBT $n = 74$, CAU $n = 66$) responded to those administered 18 months postnatally. We obtained neonatal data on 243 newborns (86%; CBT $n = 121$, CAU $n = 122$). In total, 184 participants (65%; CBT $n = 89$, CAU = 95) provided data on mother–infant bonding. We assessed 192 children (68%; CBT $n = 94$, CAU $n = 98$) using the CBCL/C-TRF at, on average, 18.5 months of age (s.d. = 1.5), and 175 children (62%; CBT $n = 90$, CAU $n = 85$) were administered the BSID-III at, on average, 22.0 months of age (s.d. = 2.7). Losses to follow-up for the CBCL and the BSID were independently predicted by the presence of a baseline maternal comorbid disorder (depression with anxiety or PTSD), missing STAI and EPDS results at 18 months were predicted by higher baseline STAI scores, missing mother–infant bonding data were predicted by low SES and high baseline STAI scores, and missing values for neonatal outcomes by higher SES. After multiple imputation, intention-to-treat analyses were performed among 140 women in the CBT and 142 in the CAU group. Table 2 demonstrates follow-up time-specific differences in mean levels of anxiety and depression between the randomised groups, none of which were statistically significant except for those at 24 weeks' gestation. At that time the CBT group showed higher mean levels for anxiety in particular, but also for depression compared with the CAU group. These differences were statistically significant and corresponded to effect sizes (Cohen's *d*) of 0.41 and 0.25 respectively.

Table 3 displays the child outcomes and the quality of mother–infant bonding according to treatment group. We observed no statistically significant differences or differences with clinical or scientific relevance for any of these measures. Also, we did not observe such differences in treatment effects across the stratification variables.

Subgroup analyses according to DSM-IV diagnosis showed a statistically significant interaction result only for birth outcomes. Among women with an anxiety disorder ($n = 98$, including 14 with PTSD) the infant's gestational age at delivery was lower (mean difference: −1.0 (95% CI −1.9 to −0.2)) in the CBT group compared with the CAU group. This treatment effect was statistically different from the other DSM-IV subgroups (*P* for interaction: 0.048). After adjusting for birth weight, the negative effect on gestational age at delivery disappeared. The *post hoc* subgroup analysis according to baseline symptom severity threshold did not show any substantial or statistically significant differences.

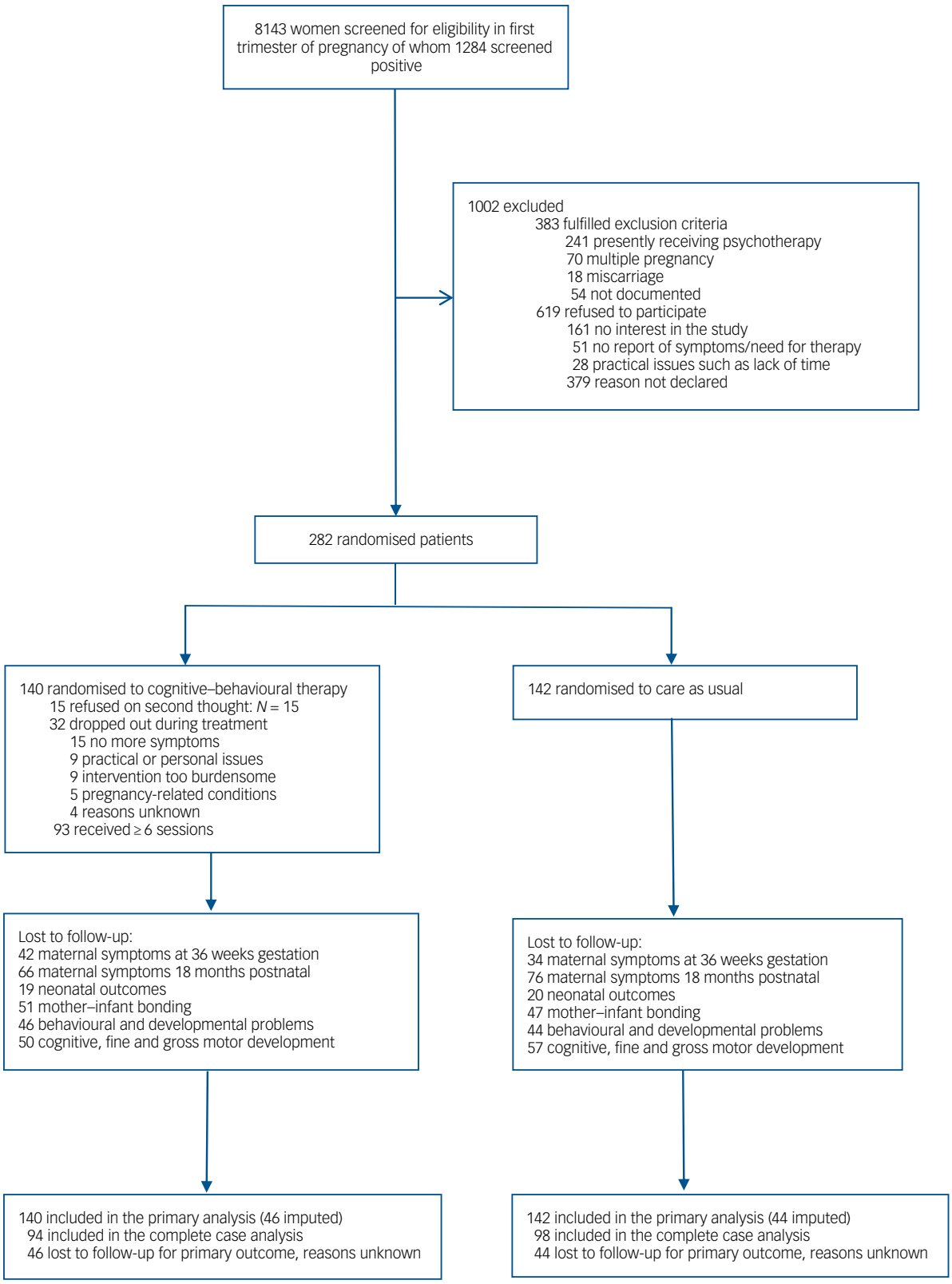

Fig. 1 Participant flow through the The PRegnancy Outcomes after a Maternity Intervention for Stressful EmotionS (PROMISES) randomised controlled trial.

Table 1 Baseline characteristics of participants according to treatment group[a]

	CBT (n = 140)	CAU (n = 142)
Age, years: mean (s.d.)	33.4 (4.6)	32.1 (4.5)
Multiparous, *n/N* (%)	70/140 (50.0)	73/142 (51.4)
Marital status: single, *n/N* (%)	12/136 (8.8)	10/136 (7.4)
Ethnicity: Black and minority ethnic, *n/N* (%)	8/134 (6.0)	3/136 (2.2)
Smoking, *n/N* (%)	11/89 (12.4)	11/100 (11.0)
Use of antidepressants, *n/N* (%)	2/140 (1.4)	2/142 (1.4)
Socioeconomic status, *n/N* (%)		
Low	48/140 (34.3)	51/142 (35.9)
Moderate	36/140 (25.7)	35/142 (24.6)
High	56/140 (40.0)	56/142 (39.4)
STAI score, mean (s.d.)[b]	48.6 (8.7)	48.5 (8.4)
EPDS score, mean (s.d.)[b]	9.8 (4.1)	9.7 (4.1)
STAI score ≥42, *n/N* (%)[b]	120/138 (87.0)	119/137 (86.9)
EPDS score ≥12, *n/N* (%)[b]	45/135 (33.3)	43/137 (31.4)
DSM-IV diagnosis, *n/N* (%)		
Anxiety	48/138 (34.8)	36/142 (25.4)
PTSD	9/138 (6.5)	5/142 (3.5)
Depression	14/138 (10.1)	9/142 (6.3)
Comorbid anxiety and depression	12/138 (8.7)	12/142 (8.5)
Comorbid PTSD and depression	2/138 (1.4%)	8/142 (5.6)

CBT, cognitive–behavioural therapy; CAU, care as usual; STAI, State–Trait Anxiety Inventory; EPDS, Edinburgh Postnatal Depression Scale; PTSD, post-traumatic stress disorder.
a. Based on complete data.
b. Higher values indicate more severe symptoms.

In all analyses, adjustment for baseline diagnosis or following a complete case approach did not materially affect the results. Likewise, the per protocol approach to analyses showed no different outcome patterns.

Discussion

Main findings

We found no beneficial effect of prenatally initiated CBT for anxiety, including PTSD, and depression during pregnancy on mother or child compared with CAU. Surprisingly, we observed that CBT increased maternal symptoms of anxiety and depression mid-pregnancy. *Post hoc* analyses revealed an indication for adverse effects of CBT on the infant's gestational age at delivery when mothers had anxiety disorder or PTSD.

Comparison with findings from other studies and interpretation

Our findings contrast with those from a large meta-analysis that concluded that CBT is effective for preventing and treating perinatal maternal depression.[5] Although publication bias was suggested, this could not fully explain the findings. Regarding perinatal anxiety, a systematic review identified only one RCT on CBT and this study did not find an effect.[24] There are several possible explanations for the absence of an effect on maternal symptoms in our study. First and foremost, the women were not seeking help and patient engagement in CBT is a powerful predictor of its effectiveness.[25] Cuijpers *et al* reported that, in patients recruited through systematic population screening rather than referral, effect sizes of psychological treatments for depression were relatively low.[26] The investigators offered several explanations for this phenomenon, including the participants' expectation that treatment would not be effective in their situation or that symptoms would diminish anyway, expectations that may well be associated with pregnancy. Second, the effects of CBT have shown to be most robust in groups at high risk of perinatal mental illness, including multiparous, Black and minority ethnic and single women.[5] These constituted less than 10% of the participants in our study and therefore our study population can be considered low risk. Third, participation in the study can be considered an intervention in itself and may have reduced symptoms in both groups, thereby causing a floor effect.[27] Fourth, more psychological care by the GP in the control group relative to the CBT group could have reduced the apparent effect. However, this seems unlikely because in The Netherlands, GPs diagnose psychosocial problems less frequently during pregnancy than outside pregnancy[28] and because roughly similar decreases in depressive symptoms were found in the control groups of comparable studies.[8,9] In our view, a combination of the aforementioned factors may have brought about the lack of improvement in maternal symptoms.

We found no effect on mother–infant bonding or on child outcomes. This is congruent with the maternal results and additionally suggests no effect of CBT on the offspring through other pathways

Table 2 Anxiety and depression symptom levels according to follow-up time and treatment group[a]

	n_{CBT}/n_{CAU}	CBT (n = 140), mean (s.d.)	CAU (n = 142), mean (s.d.)	Mean difference[a] (95% CI)	z	P
STAI score[b]						
Baseline (at 12 weeks' gestation)	138/137	48.6(8.7)	48.5 (8.4)	0.0 (–2.0 to 2.0)		
24 weeks' gestation	115/120	47.7 (11.5)	43.2 (10.9)	4.5 (2.0 to 7.0)	3.54	<0.001
36 weeks' gestation	98/108	43.2 (10.6)	41.5 (12.6)	1.5 (–1.2 to 4.2)	1.09	0.275
6 weeks postnatal	94/83	40.9 (11.5)	41.4 (13.5)	–1.4 (–4.4 to 1.5)	–0.95	0.342
3 months postnatal	76/87	43.8 (13.7)	41.1 (12.4)	2.2 (–0.9 to 5.4)	1.38	0.167
6 months postnatal	91/97	42.1 (13.6)	40.8 (11.7)	0.9 (–2.2 to 4.1)	0.58	0.560
12 months postnatal	79/75	41.0 (12.8)	41.4 (12.4)	0.7 (–2.9 to 4.3)	0.39	0.697
18 months postnatal	72/66	40.9 (11.3)	40.1 (10.2)	1.5 (–2.4 to 5.4)	0.74	0.460
EPDS score[b]						
Baseline (at 12 weeks' gestation)	135/137	9.8 (4.1)	9.7 (4.1)	0.1 (–0.9 to 1.1)		
24 weeks' gestation	120/120	10.4 (5.0)	9.2 (4.7)	1.2 (0.2 to 2.1)	2.43	0.015
36 weeks' gestation	97/104	9.4 (4.6)	8.3 (4.6)	0.8 (–0.2 to 1.8)	1.49	0.136
6 weeks postnatal	90/88	8.4 (4.6)	8.4 (4.9)	–0.1 (–1.2 to 1.0)	–0.20	0.844
3 months postnatal	74/88	8.7 (5.4)	8.2 (4.7)	0.3 (–1.0 to 1.5)	0.44	0.660
6 months postnatal	87/95	8.0 (5.3)	8.3 (5.3)	–0.3 (–1.6 to 1.0)	–0.46	0.647
12 months postnatal	75/77	7.9 (5.0)	7.8 (5.2)	0.5 (–1.0 to 1.9)	0.67	0.504
18 months postnatal	74/63	7.8 (5.0)	7.4 (4.1)	0.9 (–0.7 to 2.6)	1.12	0.263

CBT, cognitive–behavioural therapy; CAU, care as usual; n_{CBT}/n_{CAU}, numbers in CBT and CAU groups respectively; STAI, State–Trait Anxiety Inventory; EPDS, Edinburgh Postnatal Depression Scale.
a. Means (s.d.) are based on complete data, mean differences between groups were quantified with linear mixed-effects models using all available data with follow-up time as a categorical independent variable.
b. Higher values indicate more severe symptoms.

Table 3 Child outcomes and quality of mother–infant bonding according to treatment group[a]

	n_{CBT}/n_{CAU}	CBT ($n = 140$), mean (s.d.)	CAU ($n = 142$), mean (s.d.)	Mean difference[a] (95% CI)	*t*	*P*
Neonatal outcomes						
Birth weight, g	123/120	3413 (647)	3457 (561)	−53.5 (−196.3 to 89.2)	−0.74	0.462
Gestational age at delivery, weeks	122/121	38.5 (2.3)	38.8 (1.8)	−0.3 (−0.8 to 0.2)	−1.23	0.217
Apgar score at 1 min[b]	111/116	8.6 (1.4)	8.5 (1.3)	0.1 (−0.3 to 0.4)	0.37	0.710
Apgar score at 5 min[b]	121/120	9.5 (1.0)	9.5 (1.0)	−0.1 (−0.3 to 0.2)	−0.41	0.680
Child development (BSID-III)[c]						
Cognitive score	90/85	11.6 (2.2)	11.9 (2.0)	−0.27 (−0.88 to 0.33)	−0.89	0.376
Fine motor score	90/85	11.5 (2.6)	11.7 (2.6)	−0.27 (−1.03 to 0.50)	−0.69	0.492
Gross motor score	90/85	9.6 (2.4)	9.7 (2.4)	−0.08 (−0.78 to 0.63)	−0.21	0.835
Child behaviour (CBCL/1.5–5)[d]						
Internalising problems	94/98	4.6 (3.4)	3.9 (3.1)	0.76 (−0.11 to 1.63)	1.73	0.085
Externalising problems	94/98	10.1 (5.6)	9.6 (6.3)	0.39 (−1.12 to 1.91)	0.51	0.609
Total problems	94/98	21.8 (11.6)	19.8 (12.5)	1.38 (−1.82 to 4.57)	0.85	0.399
Mother–infant bonding (PBQ)[e]						
Total score	89/95	105.1 (5.1)	105.6 (5.4)	−0.3 (−1.8;1.2)	−0.34	0.733

CBT, cognitive–behavioural therapy; CAU, care as usual; n_{CBT}/n_{CAU}, numbers in CBT and CAU groups respectively; BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; CBCL/1.5–5, Child Behavior Checklist for Ages 1.5–5; PBQ, Postpartum Bonding Questionnaire.
a. Means (s.d.) are based on complete data, mean differences between groups were quantified with linear regression models using multiply imputed data and are adjusted for parity and socioeconomic status.
b. Higher values indicate better neonatal health.
c. Higher values indicate better performance.
d. Higher values indicate higher severity of problems.
e. Higher values indicate a more problematic mother–infant bond.

than maternal symptoms, for example stress hormones.[2] Our findings in the offspring concur with those from the only other comparable study ($n = 528$), which showed no effect of modified CBT on cognitive, socioemotional or physical developmental outcomes in children, although they did find a positive effect on the mothers.[6] By contrast, the remaining studies – a small RCT ($n = 54$, data on 29 infants),[7] a pilot study ($n = 25$)[8] and a study including women with diabetes and depression ($n = 34$)[9] – showed encouraging effects of CBT on maternal symptoms and child development. This might be because these studies included higher-risk groups, i.e. all women fulfilled DSM criteria for depressive disorder or were screened using a higher EPDS cut-off than we used,[7–9] were (in part) referred to the study[7–9] or had a physical illness.[9] However, small samples limited the evidence.

We surprisingly found slight indications for unintended effects of CBT, i.e. an increasing effect mid-pregnancy on anxiety in particular, but also on depression. As far as we know, this is unprecedented. The increase in anxiety may have resulted from the exposure component of CBT.[29] Exposure to fear-evoking stimuli may increase levels of anxiety in the short term and cause physiological stress reactions.[30] These reactions may in turn adversely affect intrauterine development of the offspring.[2] Such a mechanism may have caused the adverse effect we found on the infant's gestational age at delivery in the subgroup of 98 women with anxiety disorders, including PTSD, a group of disorders that may reflect a particular sensitivity to the exposure component of CBT. Whereas potential risks of antidepressants during pregnancy are well researched, risks of psychotherapeutic interventions have, to our knowledge, not been addressed in perinatal studies. Because many more women at baseline screened positive for anxiety symptoms or disorder, including PTSD, rather than depressive symptoms or disorder, this finding may have relevance and in our view calls for more work on anxiety in pregnancy.

Clinical considerations

Our results are not in line with leading guidelines. In those from the APA and ACOG,[10] and the Australian Clinical Practice Guideline on mental healthcare in the perinatal period,[11] unselective screening for depression and anxiety is advised at first contact with primary care during pregnancy and the early postnatal period, followed by, for example, CBT if indicated. Likewise, in the evidence report and systematic review for the US Preventive Services Task Force, universal screening is recommended for depression in pregnant and postpartum women.[12] The findings of our study, however, do not indicate that a screen-and-treat approach to non-help-seeking pregnant women at low risk of mental illness from the general population is effective for the mother; furthermore, our study suggests that CBT during pregnancy may have no beneficial effects on offspring. Our study may further implicate the need for a comprehensive assessment, including the pregnant woman's commitment, before offering a high-intensity psychological intervention.

Limitations and strengths of this study

We included 192 (74%) rather than the required sample size (260) in our complete case analyses, which may have caused some attrition bias and reduced statistical power. Consequently, to include all 282 participants in the intention-to-treat analysis we had to use multiple imputation, which is the preferred method to deal with missing values, including missing values for outcome variables, although the MAR assumption cannot be checked.[23] A further limitation may be that we included women who were not actively seeking help and therefore, although they accepted it, may have been not ready for psychological treatment. This is suggested by the moderate response rate among those fulfilling inclusion criteria and the dropping out of 15 women shortly after randomisation to CBT. Further, the fact that the women in our study were not help-seeking may have limited the potential to reduce symptoms by the CBT as well as generalisation of our findings to pregnant women who do seek help. Future studies could assess women's baseline expectations and commitment to the treatment and study the relation of these factors to effectiveness. Further, we included a low-risk population with relatively few multiparous, Black and minority ethnic and single women, which may also have contributed to our null findings. Future research may therefore additionally include women from higher-risk groups. Finally, the results from our subgroup analyses must be interpreted very cautiously as they are prone to problems such as false-positive results from multiple testing and low power. Consequently, they require replication in future studies.

Strengths of our study include its size, the use of a range of child outcome measures, the implementation of a manualised CBT intervention by trained CBT psychologists, and supervision of the CBT

therapists to monitor treatment integrity. In addition, our broad inclusion criteria and sampling from the general population probably increase generalisability.

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Data availability

H.B. and T.V. have ongoing full access to the study data, without any restriction.

Authors' contributions

H.B., T.V., J.L.A.-M., J.O., M.G.v.P. and C.L.H.B. formulated the research question(s); H.B., T.V., J.L.A.-M., J.O., M.G.v.P. and C.L.H.B. designed the study; H.B., T.V., J.L.A.-M., C.B., B.W.M., M.G.v.P. and C.L.H.B. carried out the study; H.B., T.V., S.D.H. and C.L.H.B. were involved in analysing the data; and all authors were involved in writing the article.

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