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Stormy clouds in seventh heaven

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Pregnancy Outcomes after a Maternity Intervention for Stressful EmotionS: the PROMISES study.

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chapter 6

Abstract

Background

There is ample evidence from observational prospective studies that maternal depression or anxiety during pregnancy is a risk factor for adverse psychosocial outcomes in the offspring. However, to date no previous study has demonstrated that treatment of depressive or anxious symptoms in pregnancy actually could prevent psychosocial problems in children. Preventing psychosocial problems in children will eventually bring down the huge public health burden of mental disease. The main objective of this study is to assess the effects of cognitive behavioural therapy in pregnant women with symptoms of anxiety or depression on the child's development as well as behavioural and emotional problems. In addition, we aim to study its effects on the child's development, maternal mental health, and neonatal outcomes, as well as the cost-effectiveness of cognitive behavioural therapy relative to usual care.

Design

We will include 300 women with at least moderate levels of anxiety or depression at the end of the first trimester of pregnancy. By including 300 women we will be able to demonstrate effect sizes of 0.35 or over on the total problems scale of the child behavioural checklist 1.5-5 with alpha 5% and power (1-beta) 80%.

Women in the intervention arm are offered 10-14 individual cognitive behavioural therapy sessions, 6-10 sessions during pregnancy and 4-8 sessions after delivery (once a week). Women in the control group receive care as usual.

Primary outcome is behavioural/emotional problems at 1.5 years of age as assessed by the total problems scale of the child behaviour checklist 1.5 – 5 years. Secondary outcomes are mental, psychomotor and behavioural development of the child at age 18 months according to the Bayley scales, maternal anxiety and depression during pregnancy and postpartum, and neonatal outcomes such as birth weight, gestational age and Apgar score, health care consumption and general health status (economic evaluation).

Trial Registration: NTR2242

Background

The burden of mental disorders is huge and at least comparable to the burden caused by many severe physical diseases. In the WHO Global Burden of Disease project it was estimated that 50% of all daily adjusted life years (DALY's) in the 15-44 years old are due to nine psychiatry-related conditions¹. Depressive disorders are projected to rank second on a list of 15 major diseases in terms of burden of disease in 2030². In addition, a substantial part of the costs are caused by new cases, which accounts for 39.2% of the costs at population level³. Therefore, prevention of mental disorders is essential.

Maternal anxiety or depression during pregnancy is an important and potentially modifiable risk factor for cognitive, behavioural and emotional problems among the offspring children⁴⁻⁹. Around 10-20% of all women are suffering from depression or anxiety during pregnancy¹⁰⁻¹³. The magnitude of the effects of maternal anxiety or depression on the child's psychosocial problems is considerable: it is estimated that up to 22% of the variance in behavioural problems is linked with prenatal anxiety, stress or depression⁶. The adverse effects seem to be lasting. For example, antenatal anxiety of the mother was related to behavioural or emotional problems of 4 year old children, independent of the mother's postnatal depression or anxiety⁴, and higher anxiety levels of the mothers early in pregnancy were related to an increase in ADHD and other externalizing problems in their 8-9 year old children¹⁴.

There are several mechanisms through which depression or anxiety during pregnancy could have an adverse effect on the offspring. These mechanisms can be divided into direct and indirect. A direct mechanism that has been researched for decades is one in which depression or anxiety activates the maternal stress system leading to elevated glucocorticoid levels, which subsequently influence the development and long-term physiology of the foetus' brain by passing the placenta. This direct mechanism falls under the rubric of "early life programming" and has been a popular hypothesis for the explanation of not only brain disorders but has been suggested to play a role in cardiovascular disease as well¹⁵. Further, epigenetic variation has been proposed as a mediating mechanism in linking early life exposures to long-term psychological and behavioural outcomes¹⁶.

The effect of maternal stress on the developing foetus might also be indirect. Women who suffer from antenatal depression have the tendency to take less good care of themselves (e.g. neglecting personal hygiene, the occurrence of sleeping problems, disturbed drinking and smoking habits, denying prenatal care). These consequences might all influence the

development of the foetus¹⁷⁻²⁰. Another indirect way in which depression might influence the mental development of the offspring is when the antenatal depression remains after delivery and turns into a postnatal depression. In this way, mother-child attachment might be endangered, because the mother has a reduced ability to respond to the child. Children from depressed mothers have a higher risk of insecure attachment, which in turn is associated with cognitive, behavioural and emotional problems^{1,21-23}. In addition, the association between antenatal depression and adverse outcomes in the offspring might be indirect because it could be explained by a shared genetic predisposition between mother and child.

Whatever the actual mechanisms involved are, there is presently convincing evidence that children whose mothers suffered from anxiety or depression during pregnancy constitute a high risk group for behavioural and emotional problems. On population level, substantial total mental health gains may be accomplished when depressed or anxious women are adequately treated during their pregnancy, even if the effect size of the treatment is relatively small.

The effectiveness of psychological therapy in the treatment of both depression and anxiety has been shown during the past 50 years, especially for cognitive behavioural therapy (CBT)²⁴⁻²⁸. Although guidelines state that medication is an alternative effective treatment, the safety of antidepressants during pregnancy remains insecure²⁹. Still, it is too early to implement CBT for depressed or anxious women to prevent psychosocial problems in the offspring. This is because in the development of such a preventive strategy, demonstration of the causality and size of the effect of the reduction of symptoms of depression and anxiety on child outcomes is a crucial step, a step that has not been taken to date. This knowledge gap will be filled by the results of the present experimental study.

We are currently performing a randomized controlled trial (RCT) among pregnant women with symptoms of depression or anxiety to study the effect of CBT as compared to care as usual (CAU) on the offspring's behavioural and emotional problems. In the CBT arm, we expect more beneficial neonatal outcomes, in particular higher birth weight and less prematurity, which are risk factors for adverse cognitive and behavioural outcomes themselves⁸. We also anticipate reduced smoking and less drinking, with many physical and mental health benefits for the child as a result²⁰. Since prenatal depression has shown to be related to postnatal depression, we hypothesize that our intervention will also counter postnatal depression, which in turn will benefit the mother – child attachment³⁰.

Finally, but not unimportantly, the reduction of symptoms of anxiety or depression during pregnancy and the early postnatal period is valuable in itself. CBT may further provide

for a safer approach to reducing symptoms in pregnancy than antidepressant medication²⁹. To date, no such study has been performed as far as we are aware of.

Design

Objective

The aim of the present study is to examine the effect of CBT in women with at least moderate symptoms of anxiety and/or depression at the end of the first trimester of pregnancy, on the extent of total behavioural and emotional problems in their children at 1.5 years of age, as compared with CAU.

Setting

The source population consists of all pregnant women in the Netherlands in the first trimester of their pregnancy. Women are recruited in primary, secondary and tertiary obstetric care. Women are screened for anxiety and depression symptoms at the end of the first trimester of pregnancy. Women with at least moderate symptoms of anxiety and/or depression are either randomized to the intervention group in which they receive 10-14 sessions of CBT, or to the control group in which they receive care as usual. Figure 1 shows the detailed design of the study.

Study outcome measures

The primary outcome in this project is the total emotional and behavioural problems score of the child according to the Child Behaviour Check List 1.5 – 5 (CBCL 1.5-5) at 18 months of age. Secondary outcomes are the child's mental and psychomotor development at 18 months of age, the change in depressive and anxious symptoms in the mother, obstetric variables such as birth weight, gestational age and Apgar score, the socio-demographic and lifestyle factors, such as alcohol use, smoking and education, and cost-effectiveness of the therapy.

Sample size

Studies on the prevention of mental disorders tend to suffer from problems of insufficient statistical power³¹. In the current study we aimed to get around this problem by using a continuous primary outcome measure and by including a high risk group, i.e. selective

prevention.

We decided that effect sizes of 0.35 (midpoint of small – medium effect size) or over on the total problems scale of CBCL 1.5-5 are to be detected. With alpha 5% and power (1-beta) 80%, we have to include 260 participants in our analyses. To account for some drop out we aim at 300 women entering the trial. If 50% eventually meets all criteria and gives informed consent, 600 screen-positives must be identified. The 50% rate is based on studies with psychological interventions during pregnancy aimed at reducing the occurrence of postnatal depression³⁰. Given the figures in the literature^{32,32} we can expect amply 10% screen-positives on either the anxiety or depression screener. With an estimated 50% comorbidity between anxiety and depression this means that approximately 15% are eligible for the randomisation. Therefore, 4,000 women needed to be screened. Assuming a response rate of 75%³³ this implicates that 5,333 women must be offered screening. To be on the safe side, we aimed at screening 6,000 women. During the trial it appeared that only 25% rather than 50% of all screen-positive women meets all criteria and gives informed consent. Therefore, we adjusted the number needed to screen for including 300 women to approximately 12,000.

Inclusion

Women in obstetric care in the Netherlands with a significant level of anxiety (6 item STAI ≥ 42) or at least moderate depressive symptoms (EPDS ≥ 12) in their first trimester were invited to participate in the trial.

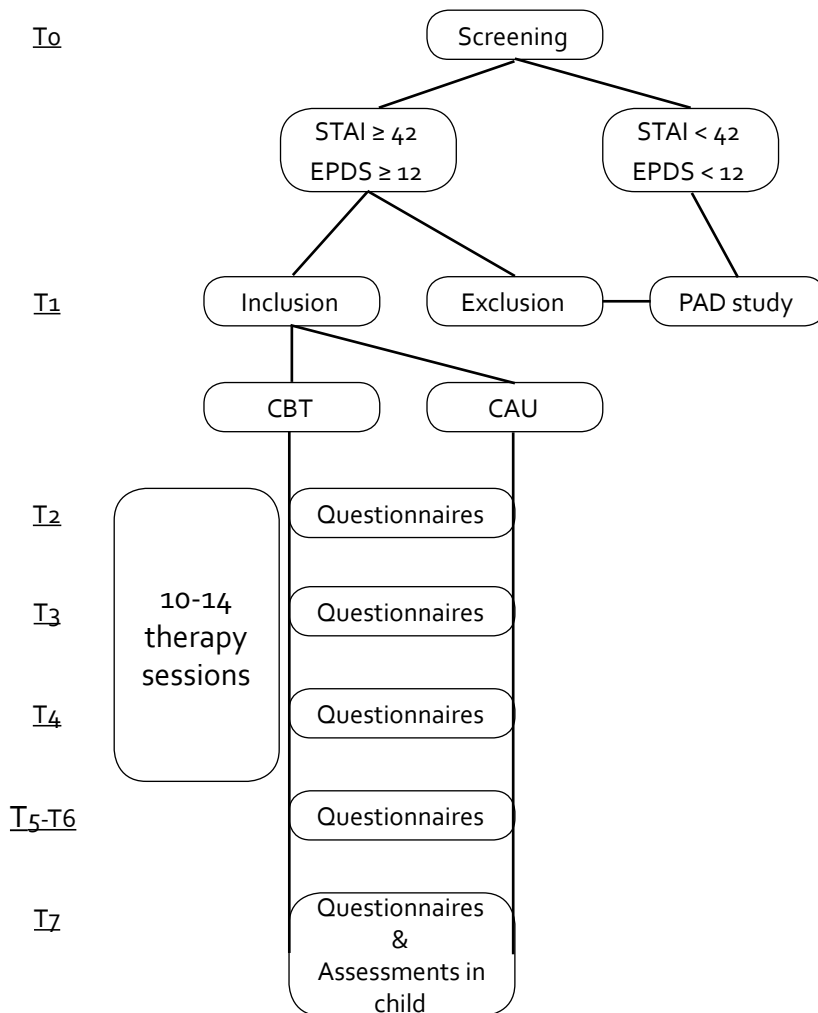
Exclusion

Women fulfilling one or more of the following criteria are excluded from participation:

1. Multiple pregnancy. We decided to exclude women with multiple pregnancy as they have a markedly increased obstetric risk; their inclusion would threaten the homogeneity of the study population and thereby decrease the sensitivity to detect effects.
2. High suicidal risk according to the suicidality subscale score on the MINI International Neuropsychiatric Interview (MINI, defined as a positive response on the question on concrete suicide plans)
3. Presently receiving psychotherapy
4. Substantial physical disease or illegal substance abuse
5. No mastery of the Dutch language
6. Having a psychiatric history on bipolar disorder, psychoses and manic disorder
7. History of in vitro fertilization

Due to a lower than expected response rate after commencement of the trial we decided to also include participants in hospitals to increase the eligible study population, as opposed to only including participants in primary care. This implied that we decided to no longer exclude multiple pregnancies and women with a history of in vitro fertilization.

Figure 1 Flow diagram



Assessments

Participating women are asked to fill out questionnaires until their child is 1.5 years. This is done at eight time points: the screener at baseline (T₀), the additional baseline information (T₁), and follow-up questionnaires at 24 and 36 weeks of gestation (T₃ and T₄), at 6 weeks postpartum (T₅), 6 months postpartum (T₆), 12 months postpartum (T₇) and 18 months postpartum (T₈).

At each time point, the levels of anxiety and depression are monitored by the STAI and the EPDS. As depicted in table 1, all other questionnaires are filled out once or at several time points. For anxiety, we use the Dutch version of the 6-item State Trait Anxiety Inventory (STAI). This self-report questionnaire is as valid as the full 20-item version and has frequently been used to measure antenatal anxiety³². For the screening on depression we use the Edinburgh Postnatal Depression Scale (EPDS), which has 10 items³⁴. This is the most frequently used self report depression screener in the postnatal period as well as during pregnancy and has been found particularly valid during pregnancy because this scale omits somatic symptoms³³.

The following information is obtained from participants. The exact time of administration of the corresponding instrument can be found in figure 2.

- Life events before pregnancy are assessed at baseline, using the Negative Life Events Questionnaire (NLEQ)³⁵.
- Perceived social support is measured according to the 9-item Social Support Questionnaire (SSQ)-short form³⁶.
- General health, socioeconomic position, ethnicity, smoking behavior, alcohol use, psychiatric history (whether the participant has had depression and/or anxiety symptoms before, whether she was treated for this and whether she is presently in treatment for these symptoms is assessed. Socioeconomic position is measured using five indicators: family income, educational level (father and mother), and occupational level (father and mother). This questionnaire is based on a questionnaire used in the Utrecht Health Project (Dutch acronym LRGP: Leidsche Rijn Gezondheids Project, www.lrgp.nl). General health status will also be taken into account according to the EQ-5D³⁷.
- Personality is assessed using the NEO Five Factor Inventory (NEO-FFI). The NEO-FFI is a shortened version of the NEO-PR-I³⁸ and covers the Big Five of personality (neuroticism, extraversion, openness, altruism and conscientiousness). These aspects each contain 6 subscales. The NEO-FFI contains 60 questions, 2 on each subscale. The present study will add 4 full subscales to the short version; two subscales of neuroticism, one

of extraversion and one of conscientiousness. This is because we expect them to have the strongest association with persistence of depression and/or anxiety. The NEO-FFI is translated and validated in Dutch³⁹.

- Information on previous pregnancies, family size and composition, pregnancy related life events and on reactions on becoming a parent is gathered using questionnaires from the ALSPAC study (www.bristol.ac.uk/alspac).
- Suicide risk is measured using six screening questions from the MINI International Neuropsychiatric Interview⁴⁰.
- Maternal attachment style is measured according to the ECR⁴¹, which has been translated and validated for the Netherlands by Conradi et al.⁴².
- Health care consumption is assessed based on the TIC-P⁴³. This instrument allows reliable recall over the past 6 months⁴⁴.
- Coping style is assessed using the Utrechtse Coping Lijst, the UCL⁴⁵.
- A Dutch version of the Dysfunctional Attitude Scale (DAS) is used to measure cognitions and attitudes⁴⁶.
- Obstetric variables such as gestational age, birth weight, Apgar score, complications such as (pre)eclampsia or HELLP, which is obtained from midwives. Women are asked to give consent for this.
- Finally, we use the SCID-II to screen for a possible clinical depressive or anxiety disorder⁴⁷. The SCID-II is the only questionnaire used that has to be taken in a personal interview.

Besides questionnaires for the mother during her pregnancy and the first 1.5 years postpartum, there are assessments of the child at 1.5 years of age. One of the assessments concerns the Bayley Scale of Infant Development (BSID-II)⁴⁸. This is a formal neuropsychological tool to assess the developmental level of a child between 1 and 42 months. It is individually administered by one of the researchers and consists of 3 subscales: cognitive development (mental development index), gross and fine motor development and the behavioural rating scale. This tool is widely used in both research and clinical settings and is considered the best and most applied method for the assessment of the child's development to date⁴⁹. Importantly, the instrument has shown to be sensitive. In the context of our proposal, maternal anxiety in pregnancy explained as much as 11% of the variance in the Bayley scores in a study among two year old toddlers by LaPlante et al.⁵⁰.

The second assessment is the Child Behaviour Check List 1.5 – 5 (CBCL 1.5-5) including the Caregiver-Teacher Report form (C-TRF) and the Language Development Survey (LDS)⁵¹. This

well established, reliable and valid scale designed for parents and caregivers comprises seven syndrome scales: emotionally reactive, anxious depressed, somatic complaints, withdrawn, sleep problems, attention problems and aggressive problems. In addition, it contains scales for internalizing, externalizing and total problems. Symptom scores may further be related to formal DSM-diagnostic criteria. The LDS provides a screen for delays in vocabulary and word combinations.

For the assessment of psychopathology in preschool children it is essential to obtain information from different sources⁵². Therefore we decided to include the C-TRF for the caregivers of the children other than their parents. Parents are asked to hand these lists to the actual caregivers of their children, e.g. grandparents, baby-sitters, kindergarten-coaches, et cetera. Relevant in this respect, a review by Skovgaard⁴⁹ underlined the significance of both the developmental aspects (e.g. as measured with the BSID II) and the infant caregiver relation in the assessment of children 0-3 years of age.

The CBCL has been used successfully in several studies, amongst others on externalizing problems⁵⁰. It has been translated and standardized for use in around 60 countries, including the Netherlands. The CBCL 1.5-5 is considered a sensitive instrument also deployed in current intervention studies^{54,55}.

Also, mother-child interaction are measured by taping them for 15 minutes on video and scoring them afterwards on interaction points.

Additional baseline data

Women agreeing to participate are asked to provide additional baseline data at T₁, as to find in table 1. About half of these questionnaires are sent to the participants in print, the other half can be answered online. All follow-up questionnaires are available online. After providing baseline data both in print and online, women are telephoned for the Structured Clinical Interview for DSM-II Disorders (SCID-II). The SCID-II will allow us to study treatment effects additionally according to diagnostic categories rather than symptom levels.

Table 1 Assessments per measurement

	T ₀	T ₁	T ₂	T ₃	T ₄	T ₅	T ₆	T ₇
Depression (EPDS)	X	X	X	X	X	X	X	X
Anxiety (STAI)	X	X	X	X	X	X	X	X
Personality NEO-FFI		X		X		X		
Life events before pregnancy (NLEQ)		X						
Life events during pregnancy		X		X		X		
Perceived social support (SSQ)		X						
Coping styles (UCL)		X	X	X	X			
Attitudes (DAS)		X	X	X	X			
Maternal attachment (ECR)		X					X	
Quality of life (EQ-5D)		X	X	X	X	X	X	
Sociodemographic & -economic factors		X						
Lifestyle		X		X		X		
Breastfeeding						X		
General health		X						
Health care consumption		X			X	X	X	
Previous pregnancies		X						
Suicidality (MINI)		X						
Clinical Diagnostic Interview (SCID-II)		X						
Child Behaviour (CBCL)								X
Child development (BSID-II)								X

Randomisation

Right after the SCID-II interview, women are randomised 1:1 to either CBT or CAU. We will create randomisation lists, stratified for parity and socio-economic position, with randomly permuted blocks of random size. Women randomized to the CAU arm are informed about being at risk of depression or anxiety disorder by the researchers and are advised to contact their GP. A close record is kept of all care provided in the CAU arm.

CBT Intervention

The intervention consists of 10-14 individual sessions: 6-10 sessions during pregnancy and 4-8 sessions after delivery (once a week). The CBT is conducted by registered psychologists, specialized in conducting CBT.

CBT posits that an individual's biased information processing leads to maladaptive feelings and behaviours which can culminate in psychological distress and eventually in psychiatric disorders. The main focus of the proposed intervention is targeted on identifying and changing dysfunctional cognitions and schemata (attitudes) specifically for pregnant depressed and anxious patients. In CBT, the Socratic dialog is used aiming to change these dysfunctional cognitions and attitudes permanently. CBT may therefore result in long term protection against psychosocial problems. It is therefore not surprising that cognitive therapy during the acute phase of depression also appears to be effective in reducing subsequent recurrence rates²⁸.

The first session will focus on the rationale CBT, i.e. the influence of (irrational or dysfunctional) cognitions and attitudes on feelings and behaviours. Additionally, goal setting is initiated. These therapy goals are unique for each patient. The subsequent sessions are targeted at identifying and amending irrational cognitions and attitudes related to pregnancy, delivery, concerns about the (unborn) child and the future family situation. Each session will address specific pregnancy-related cognitions. Additionally, patients are taught how dysfunctional cognitions and attitudes affect adversely feelings and behaviours.

These dysfunctional cognitions and attitudes are challenged and replaced by functional cognitions and attitudes. After each session, patients are given home work. For example, patients are asked to register negative experiences, and accompanying cognitions, feelings and behaviours. Finally, in the last two to four sessions, the newly learned cognitions and attitudes are consolidated.

Data analysis

If necessary, skewed continuous variables will be transformed to normality prior to the analyses. The primary outcome, i.e. the CBCL scores at month 18, will be compared between the treatment arms using the unpaired t-test. This test will also be used for detecting differences in the Bayley scores by month 18 and the obstetric variables measured at birth. The latter group of variables will be tested using the Chi² test if categorical. Differences in attachment style at month 12 will be analyzed using analysis of covariance with the baseline variable as a covariate. Continuous outcomes that were measured more than twice (e.g. EPDS and STAI) will be analyzed as dependent variables using linear mixed models for fixed and random effects. These models are superior for the analysis of longitudinally correlated data and can optimally deal with missing values⁵⁶. A mixed model ascribes a unique intercept and slope estimate to each individual, while making use of information across individuals for predicting these quantities. In these analyses, a treatment*time variable indicating the effect of the intervention will be included as an independent variable. If despite randomisation important baseline differences exist in prognostically important variables such as the extent of social support or history of life events, they will be adjusted for. Additional analyses will be conducted to demonstrate mediation of the effect of CBT on the child's outcomes by maternal symptom level, alcohol or nicotine consumption in pregnancy, medication use or neonatal outcomes.

The analyses will primarily be carried out according to the intention-to-treat (ITT) principle, i.e. the participants will be analyzed according to their randomized allocation, regardless of the actual CBT undergone, or time in study after baseline. Aside from the optimal validity of ITT analyses, they quantify the effects on the outcome measures that would be obtained in practice. The magnitude of the effect measured in an ITT analysis incorporates the effects caused by non-adherence to CBT, behavioural changes, et cetera. Secondary analyses will be of the 'per protocol' type meaning that they will be restricted to those women that had all of the CBT sessions.

Considering specific target populations, there is evidence that the socio-economically deprived may have more benefit from treatment of depression during pregnancy¹⁸. Therefore, subgroup analyses will be undertaken according to socio-economic position. Subgroup analyses will also be undertaken according to parity.

Differences in effect of CBT between subgroups will be statistically evaluated by testing treatment by subgroup interaction terms. Effect parameters will be supplied with a 95%

confidence interval.

Economic evaluation

An economic evaluation will be conducted alongside the trial to assess the cost-effectiveness of CBT compared to care as usual in the current study population. Information on costs and health outcomes will be prospectively collected during 24 months (starting at baseline until 18 months after birth) for both mother and child. Two complementary economic analyses will be conducted. The primary outcome measure of the planned cost-effectiveness analysis is the total emotional and behavioural problems score of the child according to the CBCL at 18 months of age.

In the additionally planned cost-utility analysis, QALYs (Quality Adjusted Life Years) will be used as the primary outcome measure. The study will be performed from a societal perspective. Medical costs that will be assessed include costs related to CBT, contacts with healthcare professionals, and medication use. Outside the healthcare sector, costs of informal care and productivity losses will be taken into account. Unit prices will largely be based on Dutch standard prices in order to facilitate comparisons with other economic evaluations. Cost-effectiveness acceptability curves will be used to inform decision-makers on the probability that the studied intervention is cost-effective.

This study protocol was approved by the medical ethical committee of the University Medical Center Groningen.

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