Received: 13 May 2022 | Revised: 23 September 2022 | Accepted: 9 January 2023

DOI: 10.1002/smi.3222

RESEARCH ARTICLE

WILEY

Can we influence the neurological development and hair cortisol concentration of offspring by reducing the stress of the mother during pregnancy? A randomized controlled trial

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Funding information

Ministry of Science and Innovation of the Spanish Government; Ministry of Science, Innovation and Universities

Abstract

The objective was to evaluate the effects of a stress management cognitive behavioural therapy followed during pregnancy on subsequent childhood on hair cortisol at birth and on neurodevelopment and Hair Cortisol Concentrations (HCC) at 6 months of age. The study sample included 48 pregnant women, divided into two groups: 24 women in the Therapy Group (TG) and 24 women who received standard pregnancy care (control group (CG); CG). To test the therapy efficacy, an evaluation of the HCC and psychological stress, psychopathological symptomatology and resilience was conducted before and after the treatment. The level of cortisol in their hair was obtained during pregnancy and that of their babies at birth. Six months after birth, a cortisol sample was taken from the hair and the babies' neurodevelopment was evaluated based on a Bayley-III test. The TG presented reductions in psychological stress and psychopathological symptomatology after treatment. On the other hand, the CG increased their cortisol concentrations between the pre and post intervention, remaining stable in the TG. Moreover, results showed that TG babies had lower cortisol concentrations at birth and obtained significantly higher cognitive and motor development scores at 6 months. These findings support that providing psychological care to pregnant women may not only have a benefit on these women's mental state, but may also benefit the neurodevelopment of their offspring.

KEYWORDS

cognitive behavioural therapy, CBT, cortisol in hair, neurodevelopment, prenatal stress

1 | INTRODUCTION

Pregnancy brings about numerous changes in a woman's life at different levels and requires physical, psychological and hormonal adaptations (Alhusen et al., 2016). These psychological changes and adaptations, at the psychological level, can lead to increased stress in the mother, which may affect her health both psychologically (Puertas-Gonzalez, Mariño-Narvaez, Romero-Gonzalez, Vilar-López, & Peralta-Ramirez, 2022) and physically, for example, by increasing the likelihood of developing pregnancy-induced hypertension (Cardwell, 2013).

Similarly, maternal stress has also been associated with adverse childbirth outcomes, such as the type of childbirth or preterm birth (Chiarello et al., 2018; Glynn et al., 2008; Romero-Gonzalez, et al., 2019). In addition, maternal stress has also been shown to affect the development of the foetus (Glover, 2015) and could have consequences such as low birth weight (Chiarello et al., 2018), sleep problems (O'Connoret al., 2007) and alterations in the baby's neurodevelopment (Caparros-Gonzalez et al., 2019). Long-term effects could include an increased risk of ADHD, behavioural disorder (O'Connor et al., 2002) and an increased likelihood of neurodevelopmental disturbances in infants (Glover, 2015; Sandman et al., 2016).

On the other hand, it is well known that psychological stress is physiologically correlated with the modulation of the hypothalamic-pituitary-adrenal axis (HPA), in which cortisol's role as a mediator has been extensively investigated (Harris & Seckl, 2011; Moisiadis & Matthews, 2014). The activation of this axis involves the intervention of the hypothalamus, pituitary gland and adrenal glands. When perceiving a stressful situation, the hypothalamus secretes the corticotropin-releasing hormone (CRH), which activates the pituitary gland, producing the adrenocorticotropic hormone (ACTH), which stimulates the release of cortisol in the supra-renal glands (Tsigos & Chrousos, 2002). The hypothalamus and placenta increase the concentration of the CRH especially during pregnancy, which raises cortisol concentrations, passes through the placenta through blood circulation and reaches the foetus (Sandman et al., 2016). This increase in cortisol occurs naturally in pregnancy, and not especially due to stress.

However, increased in the mothers' cortisol has been found to be linked to changes in the offspring's cortisol concentrations, in studies both on animals and humans (Kapoor et al., 2016; Romero-Gonzalez et al., 2018). These studies show that when mothers show high cortisol concentrations during their first trimester of pregnancy, newborns present a low regulation of cortisol concentrations, which can jeopardise the maturation of certain organs, such as the lungs. In this sense, according to the Developmental Programing of Health and Disease Hypothesis (Barker, 1998; Seckl & Holmes, 2007) restrictive and adverse situations experienced during pregnancy may be likely to create unfavourable intrauterine environments. This could lead to long-term effects on the development of offspring. Therefore, both the mother's psychological stress during pregnancy and the mother's cortisol levels could have an influence on the subsequent neurodevelopment of her babies. On the one hand, a relationship has been found between an increase in perinatal stress and a greater likelihood of neurodevelopment alterations in babies (Glover, 2015; Sandman et al., 2016). On the other hand, several studies postulate cortisol levels play a key role in the formation and maturation of the foetal brain, thus being an important factor in cognitive, linguistic and motor development (Caparros-Gonzalez et al., 2019; Kingston et al., 2012). Nevertheless, there is some controversy in this regard, as some studies have found a positive association between maternal cortisol levels and offspring development, while others have found an inverse association (Sandman et al., 2016; Van den Bergh et al., 2017).

Therefore, considering the critical role of cortisol levels and perinatal stress regarding the mother, foetus and future baby as described above, different strategies have been designed to relieve stress, including stress management interventions based on Cognitive Behavioural Therapy (CBT). Although some studies have not found consistent results regarding the efficacy of CBT in reducing prenatal stress (Matvienko-Sikar et al., 2021), others have found through CBT a large reduction in maternal stress levels and psychopathological symptoms (Puertas-Gonzalez, Mariño-Narvaez, Romero-Gonzalez, Sanchez-Perez, & Peralta-Ramirez, 2022) and in the reduction of cortisol levels in saliva (Urizar & Muñoz, 2011; Zaheri et al., 2017). In addition, our research group discovered in the first part of the present study, that CBT is related to lower levels of cortisol in hair and psychological stress in pregnant women, supporting the efficacy of such evidence-based therapies on perinatal stress management (Romero-Gonzalez et al., 2020).

Therefore, given the impact of perinatal stress could have on child health, as postulated by the Developmental Programing of Health and Disease Hypothesis (Seckl & Holmes, 2007), and the effectiveness of CBT regarding stress management, the objective of this research was twofold.

On the one hand, we would like to test whether the benefits of CBT performed during pregnancy could have an impact on the infant's hair cortisol at birth and on neurodevelopment and Hair Cortisol Concentrations (HCC) at 6 months of age. For this purpose, we followed part of the participants of a previous study, where we found a reduction in HCC, perceived and pregnancy-specific stress, psychopathological symptoms and an increase in resilience in pregnant women through CBT (Romero-Gonzalez et al., 2020).

On the other hand, since this study is a follow-up of a previous study, we would like to check whether the results on CBT for stress management during pregnancy found in the full sample (reduction of psychopathology, psychological stress, HCC and increase in resilience) (Romero-Gonzalez et al., 2020), are also found in the subsample used for the present follow-up.

2 | METHOD

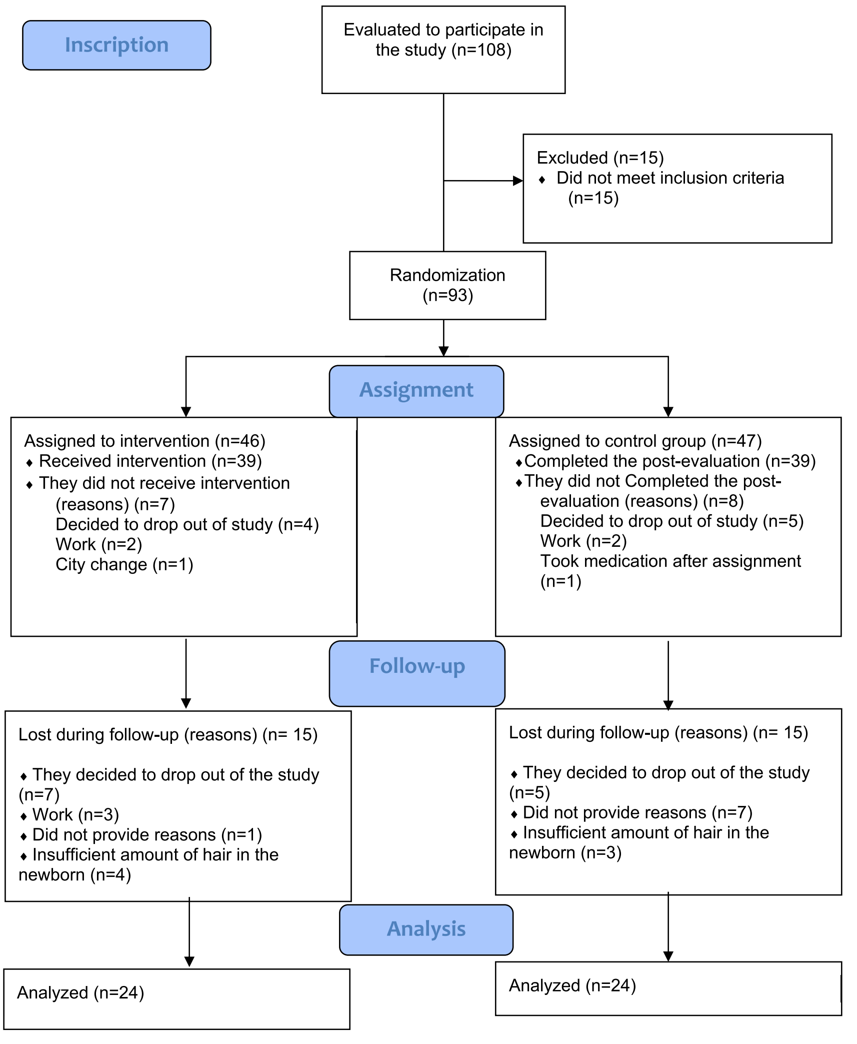
2.1 | Design

The study was a follow-up to an individual level randomized controlled trial registered as a *Clinical Trial* with the code NCT03404141.

2.2 | Participants

The study sample for the present follow-up consisted of 48 pregnant women aged between 19 and 39 years ($M = 32.65$ years; $SD = 4.26$)

FIGURE 1 CONSORT flow chart.



and their 48 babies aged 6 months (M = 6.12 months; SD = 0.34) (Figure 1). The women were recruited from the Góngora and Mirasierra health centres belonging to the Andalusian Health Service, in the province of Granada (Spain). The participants were enroled between September 2017 and May 2019, the follow-up was conducted during the months that followed ending in February 2020.

The inclusion criteria were women between weeks 12–28 of their pregnancy, with a good command of both oral and written Spanish and be over 18 years old. Week 12 was selected because at this stage of pregnancy the participant is at less risk of miscarriage. The 28th week of gestation was selected to ensure that participants would still be pregnant at the end of the intervention, so that they would have the necessary tools to face the last period of pregnancy, a period when they are usually more tired and have to start preparing for childbirth. The exclusion criteria were that of suffering from a medical or psychological illness (for example, for example, having a diagnosis of clinical depression or anxiety) or following a corticosteroid treatment.

All the women who participated in the study read the information sheet and signed the informed consent document. This document certified the confidentiality of the data collected by the evaluator and guaranteed their freedom to leave the study whenever they wished.

The study was approved by the Human Research Ethics Committee of the University of Granada (reference 881) and the Biomedical Ethics Research Committee and the Ethics Research Committee of the Health Centres, and the hospital where this study was implemented. Moreover, this study followed the guidelines of the Helsinki Declaration (Wold Medical Association, 2013) and the Good Clinical Practice Directive (Directive 2005/28/EC) of the European Union.

2.3 | Instruments

Firstly, socio-demographic and obstetric history variables that could be relevant were collected. Specifically, the following variables were collected: age, nationality, marital status, educational level, employment status, weekly hours of sport, smoking, week of gestation, first pregnancy, pregnancy planning, type of pregnancy and sex of the baby. In addition, birth weight and gestational age were also collected when the babies were born. Subsequently, psychological and cortisol levels were assessed using the instruments described below.

2.4 | Psychological evaluation

The Prenatal Distress Questionnaire (PDQ) (Caparros-Gonzalez et al., 2019): this is a 12-item self-report scale that measures pregnancy-specific stress related to maternal concerns about pregnancy, medical problems, labour and delivery, physical symptoms, bodily changes, parenting, interpersonal relations and the baby's health. Responses are given using a 5-point Likert-type scale where 0 = not at all and 4 = very much. It was used the Spanish version, which has adequate convergent validity (Caparros-Gonzalez et al., 2019). In relation to reliability, the Cronbach's alpha was 0.73 in this study.

The Perceived Stress Scale (PSS-14) (Cohen et al., 1983; Remor, 2006): this is a 14-item scale that measures general stress. Responses are given using a 5-point Likert-type scale where 0 = never and 4 = very often. Scores range from 0 to 56, and the higher the score, the greater the perceived stress. In this study the Spanish version was employed, which has showed adequate concurrent validity and sensitivity (Remor, 2006). This instrument had a Cronbach's alpha of 0.92 in this study.

The Stress Vulnerability Inventory (IVE) (Robles-Ortega et al., 2006). It consists of 22 items that evaluate the person's predisposition to feel affected by perceived stress. Therefore, it does not evaluate how much stress a person manifests, but how it affects them. The person is presented with a list of different situations and has to tick 'Yes' if the situation occurs regularly or 'No' if it does not. Items receiving an affirmative answer add 1 point. The range of scores on the scale is 0–22, higher scores corresponding to greater vulnerability to stress. Some of the items of this assessment tool include: 'Finding yourself too indecisive; spending too much time making decisions, putting aside things that need to be done' or 'Not being able to concentrate at home or at work; easily distracted by irrelevant and unwanted problems'. This instrument has demonstrated concurrent validity (Robles-Ortega et al., 2006) and the Cronbach's alpha was 0.72 in this research.

The Symptom Checklist-90-Revised (SCL-90-R) (Caparrós-Caparrós et al., 2007): this measures the subject's perceived distress in nine primary dimensions (somatisation, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism) and three global indices of psychological distress (global severity index, Positive Symptom Distress Index (PSDI) and total positive symptoms). It is a 90-item self-report inventory and items are scored using a 5-point Likert-type scale, where 1 = never and 5 = very often. This instrument has demonstrated its construct validity in its Spanish version (Caparrós-Caparrós et al., 2007). In addition, all dimensions showed an acceptable reliability, with a Cronbach's alpha ranging from 0.69 to 0.95 for the four dimensions in this investigation.

The Connor Davidson Resilience Scale, abbreviated version (CD-RISC-10) (Connor & Davidson, 2003; Notario-Pacheco et al., 2014). This instrument evaluates resilience, understood it as a person's ability to cope and adapt to their circumstances. It is composed of 10 items that are answered by a Likert-type scale with five response options ranging from 0 ('almost never') to 4 ('almost always'), which had a single dimension. Some of the items it presents are: 'I am able to adapt when changes occur 'or' I think of myself as a strong person when dealing with life's challenges and difficulties,'. The scale provides a total score ranging from 0 to 40, and higher scores indicate a higher level of resilience. The Spanish version was used, which has high construct, divergent and convergent validity (Notario-Pacheco et al., 2014). It presents good reliability, with a Cronbach's alpha was 0.87 in this study.

The Bayley Scales of Infant Development-III (Bayley-III) (Bayley, 2006): the babies' neurodevelopmental evaluation was conducted using the Bayley-III instrument. The instrument is standardised and was administered individually. It measures the development levels of children aged between 16 days and 42 months. The main objective of the Bayley-III scale is to identify any developmental problems and to provide data that is useful to plan interventions. The test is structured into three main scales: the cognitive scale, the language scale (divided into expressive and receptive communication) and the motor scale (divided into fine and gross motor skills). The Spanish adaptation of the Bayley-III scales was employed and the direct scores were transformed into Spanish percentile scores (Bayley, 2006, 2015). All domains showed an acceptable reliability, with a Cronbach's alpha ranging between 0.70 and 0.77 in this research.

The Kaufman Brief Intelligence Test (K-BIT) (Kaufman, 1990; Kaufman & Kaufman, 2009): the mothers' level of intelligence was evaluated using the K-BIT, since as has been shown, maternal intelligence is a determining factor in the early stages of infants' neuropsychological development (Forns et al., 2012). It consists of a screening test that lasts between 15 and 30 min and that aims at measuring verbal and non-verbal intelligence in boys and girls, adolescents and adults. It is divided into two subscales: vocabulary (divided into expressive vocabulary and definitions) and matrices. The Spanish version showed excellent concurrent and construct validity (Kaufman & Kaufman, 2009). In addition, all dimensions showed an acceptable reliability, with a Cronbach's alpha ranging from 0.70 to 0.73.

2.5 | Hair Cortisol Concentrations

The cortisol evaluation consisted in taking a lock of hair containing approximately 150 strands from the rear corner of the skull, as close as possible to the scalp (Sauvé et al., 2007). A maximum length of 3 cm was set for each sample to reflect cortisol concentrations during the preceding 3 months (Stalder & Kirschbaum, 2012). The samples were wrapped in aluminium foil to be adequately protected from light and humidity and were kept at room temperature until further analysis by the Department of Pharmacology of the Faculty of Pharmacy of the University of Granada. The analysis protocol was published in several studies (Caparros-Gonzalez et al., 2017; Romero-Gonzalez et al., 2018).

2.6 | Procedure

Participants were recruited by their midwives during their pregnancy's quarterly examination at the health centre. They were informed of the study at that moment and were given a phone number to call if they wished to participate. After informing them and describing the study to them, those who agreed to participate read the information sheet and gave their consent to participate.

Participants were randomly divided into two groups: a control group (CG) and a therapy group (TG). Randomisation was performed using Statisical Package for the Social Sciences (SPSS). A research assistant, who did not know the participants' data generated the random allocation sequences, registered the participants and assigned the interventions. Patients assigned to the CG received standard pregnancy care. Patients assigned to the TG attended 8 weekly, consecutive sessions of cognitive behavioural stress management therapy. Each group consisted of 4 to 5 participants lasted 1.5–2 h and were led by two trained psychologists. The intervention and control groups had the same number of participants in each edition. Thus, after the initial evaluation, the programme was implemented for 2 months, followed by a post-intervention evaluation. Then, the recruitment period started again and when the necessary participants were available, a new randomisation, evaluation and implementation of the programme was carried out. The entire procedure has been published in the first part of the present research (Romero-Gonzalez et al., 2020).

The intervention was based on the adaptation of a pre-existing treatment programme (Robles-Ortega & Peralta-Ramírez, 2006). It was a cognitive-behavioural programme that has shown to be highly effective to control stress (Linares-Ortiz et al., 2014; Navarrete-Navarrete et al., 2010; Peralta-Ramirez et al., 2009; Santos -Ruiz et al., 2017). The main objective was to provide the participants with psychological tools to gain greater control over the different stressful situations they are exposed to throughout pregnancy, allowing them to develop optimal coping strategies. The programme consisted of eight sessions divided into seven modules: (1) Psychoeducation; (2) Deactivation techniques; (3) Cognitive restructuring; (4) Alternative thought control strategies; (5) Training in social skills; (6) Relationship between anger and stress; (7) Recapitulation. All sessions had a similar structure, at the beginning of each session the participants commented on how the week had gone and the difficulties encountered in applying the techniques seen in the previous session. In this way they received feedback from the therapists. Afterwards, the technique to be worked on that week was presented and explained, and a practical exercise was carried out. At the end, the participants received a behavioural self-report so that they could write down the moments during the week when they had applied the technique, their thoughts and the difficulties encountered. The contents of the eight sessions are presented in Table 1.

On the other hand, the CG, who did not receive the intervention programme, did receive the usual care during the pregnancy process, such as attending medical check-ups with their midwife and gynaecologist or attending maternity education classes. The evaluation instruments described in the previous paragraph were delivered to both the TG and CG members at the same time. In addition, a hair sample was taken to obtain information about cortisol concentrations. Those assigned to the TG were informed of the starting date and time of their therapy. Participants of the CG were told to follow their standard routine care, which consists of three medical visits during the entire pregnancy with their midwifes. At the end of the therapy, the assessment tools described above were re-administered to participants in both groups. During this second extraction of hair, only the 2 cm closest to the root were used to avoid overlap between pre- and post-treatment samples.

TABLE 1 Intervention sessions and topics

Session name	Topics
Session 1: Psychoeducation	• What stress is, characteristics, identification of stressors, responses and consequences
Session 2: Deactivation techniques	• Thematic imagination along with diaphragmatic breathing
Session 3: Cognitive restructuring	• Cognitive distortions
Session 4: Cognitive restructuring	• Irrational beliefs
Session 5: Alternative thought control strategies	• Self-instructional training and time organisation
Session 6: Training in social skills	• Assertiveness, basic assertive rights, saying no and asking for a change of behaviour
Session 7: Relationship between anger and stress	• Emotional self-regulation
Session 8: Recapitulation	• Optimism and good humour, and recapitulation

Once the therapy sessions had ended, all the participants were contacted back during the first week after giving birth, following at that moment the established protocol (Sauvé et al., 2007). A lock of hair was taken from the newborns and kept in an aluminium foil envelope for later analysis. In those cases when newborns had not enough hair to collect, more hair is cut from the nape of the neck to obtain at least 2.5 mg. As demonstrated by other authors, HCC in newborn infants could be a good indicator of chronic stress (Hoffmann et al., 2017; Yamada et al., 2007).

To finish, 6 months after each baby's birth, the babies were evaluated using the Bayley-III test (Bayley, 2006). The evaluations were conducted at the Mind, Brain and Behaviour Research Centre at the University of Granada. They were all performed in the same room and with the same researcher. During this appointment, a hair sample was collected again from the baby.

2.7 | Data analysis

First, a comparative analysis of the sample was carried out using Student's *t* tests (continuous variables) and Chi-square (categorical variables). The objective was to check any differences between the two groups of pregnant women (CG vs. Therapy Group) based on the main sociodemographic variables, obstetric history, variables related to childbirth, as well as general maternal Intelligence Quotient (IQ).

Firstly, to test whether the results found for cognitive-behavioural therapy in the first part of the study with the full sample are also found in the sample used for follow-up, the mothers of the infants who participated in the follow-up study were included in a linear mixed repeated measures model. Group (CG and TG) and time (pre and post) were specified as main effects, and a group × time interaction was defined. Moreover, participant was entered as a random effect to account for repeated measures of the data. The dependent variables were scores in PSS, PDQ, CD-RISC-10, the SCL-90-R subscales and HCC. F-statistics and *p*-values were reported. Then, dependent *t*-tests analyses were performed on the variables presenting group*time interaction to study the differences between pre and post intervention. In addition, to check the therapy's size effect, Cohen's d was calculated: $d = 0.20$ low effect size, $d = 0.50$ medium size and $d = 0.80$ large effect size (Cohen, 1988).

Subsequently, non-parametric Mann Whitney *U* tests were performed to study any hair cortisol concentration differences between the babies born to women in the TG versus the CG group. Finally, in order to check whether there were differences between both groups (TG vs. CG) regarding the neurodevelopment of the infants at 6 months, different Mann Whitney *U* tests were performed in the different scales of the Bayley-III test (Bayley, 2006). Hedges' g was used to calculate the effect size of the differences between neurodevelopment and cortisol of infants in the two groups. In contrast to Cohen's d, Hedges' g has the inclusion of a correction factor for small sample sizes. The values used to interpret the effect size were 0.20 (small), 0.50 (moderate) and 0.80 (large) (Durlak, 2009).

Regarding the statistical analysis of cortisol in hair, a logarithmic transformation (natural logarithm; ln base e) was carried out to adjust to a normal distribution. The *t*-test, Mann Whitney test and Chi-square analyses were performed with the Statistical Package for the Social Sciences 26.0 (SPSS), while the linear mixed models were carried out using with R 4.1.3 software (R Core Team, 2022) using the *lme4* package (Douglas et al., 2015).

3 | RESULTS

3.1 | Description of participants

After performing the intervention and follow-up these women, their babies were evaluated, 24 of them belonging to the CG, with a mean age of 32.61 years (SD = 3.78) and the remaining 24 to the TG ($M = 32.71$ years; SD = 4.83).

The participant sample was found to be even with respect to the main sociodemographic variables, obstetric history, IQ and somatometric variables of the newborns (Table 2).

3.2 | Efficacy of CBT in controlling stress during pregnancy: HCC, pregnancy-specific stress, perceived stress, resilience and psychopathological symptoms

Results of analyses of participants who attended the intervention during pregnancy and completed follow-up of the infants ($n = 24$ for CG; $n = 24$ for TG), the linear mixed models results showed a statistically significant group*time interaction in: HCC [F (1,40) = 5.40; $p = 0.025$]; PDQ scores [F (1,44) = 9.14; $p = 0.004$], PSS scores [F (1,44) = 5.22; $p = 0.027$], IVE scores [F (1,42) = 5.33; $p = 0.026$], obsession-compulsion dimension of the SCL-90-R [F (1,44) = 4.99; $p = 0.030$], hostility dimension of the SCL-90-R [F (1,44) = 7.21; $p = 0.010$] and the general scales of the SCL-90-R, GSI [F (1,43) = 5.10; $p = 0.029$] and PSDI [F (1,44) = 7.00; $p = 0.011$].

The average scores of the variables showing group*time interaction in both groups in the pre and post are shown in Table 3. Subsequent between-group analyses revealed differences between CG and TG after stress therapy.

3.3 | Pre and post-intervention changes in TG and CG

Dependent *t*-tests were performed to detect changes in pre and post intervention. There were statistically pre-post intervention changes in CG in HCC, the mean score of the CG in this variable was higher after the intervention. Regarding TG, no significant statistically changes were found in the HCC, remaining stable. However, significant changes were found and the secondary outcomes: PDQ scores, PSS scores, IVE scores, obsession-compulsion dimensions of the SCL-90-R, hostility dimensions of the SCL-90-R, and on the overall scales of the GSI SCL-90-R and PSDI. The mean scores of the TG in these variables being higher before the therapy than after. No significant changes were found in the secondary outcomes in CG.

The means of the variables, the standard deviations and the analysis of differences of the GT and CG before and after the intervention are shown in Table 3.

3.4 | Neurodevelopment and baby cortisol concentration differences between the mothers in the stress management therapy group and the non-therapy group

First, Mann Whitney *U* test analyses showed statistically significant differences between TG and CG group women regarding babies' cortisol concentrations at birth ($U = 63$; $p = 0.002$; Hedges' $g = 1.13$) (Table 4).

Regarding infant neurodevelopment at 6 months of age, the results showed that there were statistically significant differences between babies born to women in the TG and babies born to women in the CG. Specifically, these differences were found for scores referring to the cognitive scale: total score, scalar, composite and percentile. In

TABLE 2 Comparison of the main sociodemographic variables, obstetric history and delivery variables, between women who attended therapy and women in the control group (CG)

		Control (*n* = 24) X(SD)/*n*(%)	Therapy (*n* = 24) X(SD)/*n*(%)	Contrast test*	*p*
Sociodemographic variables and IQ					
Age		32.61(3.78)	32,71(4.83)	−0.079	0.938
Civil status	Married/Cohabiting	24(100)	24(100)		
Nationality	Spain	21(87.5)	21(87.5)	0.003	0.955
	Immigrant	3(12.5)	3(12.5)		
Level of studies	Secondary	4(17.4)	7(29.2)	0.908	0.341
	University	19(82.6)	17(70.8)		
Employment situation	Unemployed	5(21.7)	7(29.2)	0.341	0.559
	Working	18(78.3)	17(70.8)		
Weekly hours of sport		2.67(0.72)	2.44(0.70)	0.217	0.829
Smoke	Yes	2(8.7)	-	2.180	0.140
	No	21(91.3)	24(100)		
Maternal IQ	Verbal	109.60(7.96)	109.65(8.87)	−0.012	0.990
	Non-verbal	108.60(8.53)	107.52(9.82)	0.227	0.822
	Composite	107.60(9.15)	106.48(11.8)	0.199	0.844
Obstetric variables					
Weeks of gestation	T_0	24.30(3.58)	26.08(3.91)	−1.564	0.125
	T_1	33.27(2.58)	34.08(3.93)	−0.832	0.410
Primigravida	Yes	9(39.1)	12(50)	0.561	0.454
	No	14(60.9)	12(50)		
Planned pregnancy	No	2(8.7)	4(16.7)	0.670	0.413
	Yes	21(91.3)	20(83.3)		
Type of pregnancy	Spontaneous	21(91.3)	21(87.5)	0.179	0.672
	Assisted reproduction	2(8.7)	3(12.5)		
Baby gender	Boy	13(54.2)	14(60.9)	0.216	0.642
	Girl	11(45.8)	9(39.1)		
Delivery variables					
Gestational age		39.68(0.82)	39.35(1.33)	0.984	0.332
Birth weight (g)		3188.00(459.17)	3302.75(479.39)	−0.773	0.444

Note: *The statistics reflect *t*-test for quantitative variables and Chi-square for categorical variables.
Abbreviations: IQ, Intelligence Quotient; T_0, Pre-intervention; T_1, Post intervention.

addition, with respect to the motor scale, differences were found in the total and scalar fine motor score, and in the scalar score and total gross motor skills. Moreover, differences were found in scalar, composite and percentile scores on the general motor skills scale. Among all the differences found in the variables mentioned above, 6-month-old babies born to mothers belonging to the TG obtained higher scores.

On the other hand, there were no statistically significant differences between groups in the language scale scores. The variable medians, range and the analysis of differences between both groups are shown in Table 4. In addition, the mean percentile scores for the three general scales are shown in Figure 2.

4 | DISCUSSION

The aim of this study was to test whether CBT followed during pregnancy to manage stress, has implications on hair cortisol at birth and subsequent neurodevelopment and on the capillary cortisol concentrations of the mothers' infants at 6 months of age. For this

TABLE 3 Differences in post intervention scores between Therapy Group (TG) and CG

Outcomes	Group	T_0	T_1	*t*	*p*	*d*
HHC	TG	5.04(1.12)	4.65(1.37)	1.514	0.144	0.30
	CG	5.40(0.77)	5.72(0.79)	−2.170	0.044*	0.40
PDQ	TG	17.30(5.17)	12.91(4.50)	3.561	0.002**	0.91
	CG	12.09(4.90)	12.09(3.98)	0.001	0.999	0.00
PSS	TG	24.39(7.35)	20.65(6.90)	2.189	0.040*	0.52
	CG	26.38(1.32)	26.62(1.40)	−0.849	0.411	0.17
IVE	TG	6.62(3.85)	4.71(3.22)	2.024	0.050*	0.54
	CG	4.05(4.89)	4.86(4.59)	−1.030	0.315	0.17
OBS (SCL-90-R)	TG	78.74(17.50)	66.96(26.83)	2.362	0.027*	0.52
	CG	51.59(31.41)	56.45(33.32)	−0.859	0.400	0.15
HOS (SCL-90-R)	TG	56.52(26.69)	40.00(32.05)	2.133	0.044*	0.56
	CG	36.14(27.03)	44.32(29.33)	−1.474	0.155	0.29
GSI (SCL-90-R)	TG	67.83(24.71)	53.70(29.00)	2.202	0.040*	0.52
	CG	39.86(29.76)	43.18(29.18)	−0.861	0.399	0.11
PSDI (SCL-90-R)	TG	49.13(23.91)	34.13(24.10)	2.562	0.018**	0.62
	CG	40.68(28.21)	46.23(23.43)	−0.946	0.355	0.21

Abbreviations: CG, Control Group; GSI, Global Severity Index; HCC, Hair Cortisol Concentrations; HOS, Hostility; IVE, Stress Vulnerability Inventory; OBS, Obsession-compulsion; PDQ, Pregnancy Distress Questionnaire; PSS, Perceived Stress Scale; PSDI, Positive Symptom Distress Index; TG, Therapy Group; T_0, Pre-intervention; T_1, Post intervention.

*Significant at the $p \leq 0.05$ level; **significant at the $p \leq 0.02$ level.

purpose, in the first part of this study related to a previous publication, we found a reduction in HCC, perceived and pregnancy-specific stress, psychopathological symptoms and an increase in resilience in pregnant women through CBT (Romero-Gonzalez et al., 2020). In the current follow-up study, we first checked whether the results found previously in the full sample were maintained in the subsample that participated in the follow-up. We then analysed the cortisol levels of the participants' infants at birth and at 6 months, as well as their neurodevelopment at 6 months.

Firstly, in relation to the results of CBT for stress management, the results for the subsample used in this study show similar reductions in psychopathological symptoms, perceived and pregnancy-specific stress and an increase in cortisol levels in the CG but not in the intervention group. Although cortisol levels vary across trimesters of pregnancy (Garcia-Leon et al., 2018), the weeks of pregnancy of the two groups were equal at both the beginning and end of the intervention. Therefore, variations in cortisol levels during pregnancy should affect both groups equally if there were no influence of therapy. However, the increase in cortisol at the post-intervention assessment was only found in the CG. Finally, we did not find an increase in resilience levels as in the previous results with the full sample (Romero-Gonzalez et al., 2020).

Secondly, with respect to cortisol levels and the neurodevelopment of babies, the results showed that the TG's babies had a lower concentration of cortisol at birth, as well as a higher level of cognitive and motor development at 6 months. However, no significant differences were found between the two groups in relation to cortisol levels at 6 months and language neurodevelopment.

Regarding the baby's cortisol concentrations, it should be noted that the babies whose mothers had attended the TG had lower cortisol concentrations at birth than the babies belonging to the CG. We hypothesise that lower infant cortisol concentrations at birth could be caused, at least partially, by the combined reduction and control of the three parameters of the mothers in the third trimester (hair cortisol, perceived stress and pregnancy-specific stress) (Kapoor et al., 2016; Romero-Gonzalez et al., 2018). On the other hand, no differences were found between the groups in cortisol levels at 6 months of age, so that the effects of CBT on mothers could have an implication on children's cortisol levels only in the short term. However, the precise mechanism by which these effects on cortisol levels are equalised between both groups of children at 6 months of age remains unknown. One hypothesis is that, from birth, children are exposed to different environments and factors (the socio-economic status of the family, the pattern of upbringing and education, the type of attachment, the child's temperament, etc.), as well as to different breastfeeding and sleeping patterns, that may affect their cortisol levels differently (Flom, et al., 2017).

On the other hand, with respect to neurodevelopment, it is worth noting that the babies of mothers who had followed the therapy showed higher cognitive and motor neurodevelopment scores. Furthermore, very noticeably with medium and large effect sizes. The results of this research are compatible with that of other studies, which

TABLE 4 Difference between neurodevelopment and cortisol levels in hair between babies of mothers who attend therapy versus mothers of the control group (CG)

			Control median (Range)	Therapy median (Range)	Mann Whitney	*p*	Hedges' g
Cortisol	Birth (ln)		7.93(3.23)	6.50(2.17)	63	0.002**	1.13
	6 months (ln)		6.28(3.98)	6.37(2.71)	116	0.722	0.34
Cognitive	Total		30(14)	32(10)	186	0.034*	0.53
	Scalar		11(15)	13(7)	155	0.006**	0.64
	Composite		105(55)	115(35)	162.50	0.009**	0.61
	Percentile		63(90)	84(70)	162.50	0.009**	0.77
Language	Responsive communication	Total	11(8)	10(4)	219	0.139	0.28
		Scalar	11(11)	11(7)	274.50	0.775	0.05
	Expressive Communication	Total	9(13)	9(8)	279	0.851	0.10
		Scalar	11(13)	11(10)	282	0.901	0.02
	Scalar		20.50(19)	21(14)	272.50	0.748	0.04
	Composite		101.50(56)	103(41)	265.50	0.642	0.09
	Percentile		54(94)	58(71)	265.50	0.642	0.15
Motor skills	Fine motor	Total	20(9)	22(78)	172.50	0.016**	0.40
		Scalar	9.50(9)	12(9)	145	0.003**	0.99
	Gross motor	Total	24(10)	25(11)	190.50	0.043*	0.64
		Scalar	8(10)	10(9)	152.50	0.005**	0.76
	Scalar		18(17)	22(15)	137.50	0.002**	0.92
	Composite		92.50(51)	107(87)	136.50	0.002*	0.63
	Percentile		30.50(91)	68(68)	121	0.001**	1.09

*Significant at the $p \leq 0.05$ level; **significant at the $p \leq 0.02$ level.

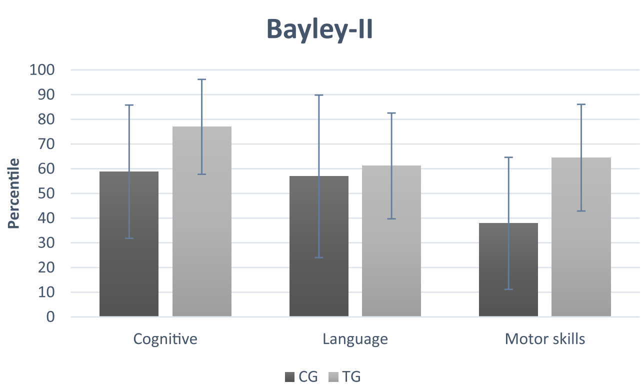


FIGURE 2 Percentile score on the general cognitive, language and motor scales of babies born to women belonging to the control group (CG) and GT. Bayley-III, Bayley Scales of Infant Development-III; CG, Control Group; TG, Therapy Group

found that high maternal cortisol concentrations were related to poorer cognitive and motor neurodevelopment in babies at 6 months of age (Buitelaar et al., 2003; Caparros-Gonzalez et al., 2019). In our study, controlling the increase in cortisol concentrations during pregnancy increased infant neurological development in these two main cognitive and motor spheres. This finding highlights the relationship between maternal cortisol and infant neurodevelopment. According to the Developmental Programing of Health and Disease Hypothesis (Arabin et al., 2021; Barker, 1998; Langley-Evans, 2006; Seckl & Holmes, 2007), changes experienced by mothers during their pregnancy condition their baby's health and subsequent development (Barker et al., 1993). In this sense, both groups of mothers (CG and TG) developed different processes during pregnancy, resulting in an improvement in stress control in TG women. This stress reduction, whose physiological correlate is defined by the mother's cortisol secretion, could have an impact on the formation of the foetal brain. Specifically, some experts indicate the importance of the HPA axis in newborn brain maturation, particularly in the development of the hypothalamus and the limbic system, which could be affected in the last moments of gestation (Rakers et al., 2017). The third trimester of gestation presents particular susceptibility to these changes. In this third trimester, the left amygdala increases its connectivity with frontal and temporal lobe regions in the foetus, this rapid development being sensitive to signals of maternal stress, as well as alterations in the maternal HPA axis; it might cause long-term neurodevelopment delays, and even different psychopathologies (Davis et al., 2018). In this way, a possible control of the increase in cortisol secretion resulting from therapy during pregnancy could mitigate future effects on brain and the neurodevelopment of newborns, at least in the short term (Arabin et al., 2021). Furthermore, the fact that the levels of psychological stress were reduced through therapy could also explain the better neurological development of the babies of these women (Glover, 2015). It is important to treat these two factors separately, as some authors found an association between cortisol levels and psychological stress, for example, Kalra et al. (2007), but others did not (Arco-Garcia et al., 2020; Romero-Gonzalez et al., 2018). Therefore, both could be independent predictors of infants' neurodevelopment (Sandman et al., 2016). On the other hand, another factor that could benefit infant neurological development was that mothers who received CBT managed their stressful situations better than mothers in the CG after childbirth and the postnatal period, resulting in better mental health, parenting behaviour and relationship with their babies. Thus, training in deactivation techniques, as well as training in the detection and transformation of cognitive distortions, together with training in social skills such as "saying no" without feeling guilty, could have provided the mother with key tools for coping with the psychological stress related to having a child. Finally, it is well known that CBT, through the acquisition of these skills, prevents emotional disturbances in the postpartum period such as postpartum depression, which could have implications for the baby (Sockol, 2015). However, further studies are needed to test these hypotheses.

However, no relationship was found with the neurodevelopment of language in any of the studies mentioned. One explanation could be the way in which language develops, that is, in a more gradual manner, with language acquisition becoming more intense at around 2 years of age (Ylinen et al., 2017). For this reason, the variability among babies regarding the language aspect was minimal and almost negligible at 6 months of age. To better examine the relationship between the mother's stress and the neurodevelopment of language, it would be necessary to evaluate language closer to the 2-year stage. It would indeed be possible to study at this latter evolutionary moment in time whether or not a relationship exists between stress reduction and language development.

This study has important implications: it is one of the first to show that a reduction in prenatal stress, as well as control of cortisol levels through CBT during pregnancy, may be associated with better neurodevelopment in offspring. Considering that the effect of prenatal stress on infant development and the regulation of neonatal stress is explained by the foetal programing of the HHA (Beijers et al., 2014; Davis et al., 2011), it is important to continue to explore desirable levels of neonatal cortisol. This could contribute to preventing subsequent diseases, and to building knowledge about neurodevelopment changes, since it has been strongly related to different disorders such as the autism spectrum or ADHD (Bhutta et al., 2002; Perou et al., 2013). In the same way, it would be interesting to follow up these babies throughout childhood to examine how foetal programing can influence later ages and detect possible changes in the neurodevelopment of language.

This investigation, however, presents some limitations. Firstly, it is important to consider that the groups had differences on some psychological variables at baseline. Still, the evident change on the remaining studied variables cannot be discredited, since its reduction due to the intervention was significant. Even though there were baseline differences between groups, the efficacy of therapy reflected in the effect sizes, demonstrate the great impact therapy can have on pregnant women. On the other hand, the sample size was reduced due to the loss of participants during the procedure. It would thus be of interest to replicate the study with larger samples and even include other variables that have not been taken into account, such as parenting patterns. In addition, although there were no statistical differences between groups with respect to socio-demographic, obstetric and delivery variables, some variations in these variables could have some influence on child comparisons due to the sample size.

To conclude, the findings of this study are novel and have a number of repercussions. On the one hand, the effectiveness of CBT has been proven once again in the field of research. In addition, the shows that CBT could be used as a measure that promotes health when applied during pregnancy, with potential benefits not only for the pregnant woman but also for her offspring.

AUTHOR CONTRIBUTIONS

Jose A. Puertas-Gonzalez: conceptualisation; methodology, formal analysis; data collection; review and editing the manuscript. **Borja Romero-Gonzalez**: methodology; data collection; review and editing the manuscript. **Carolina Mariño-Narvaez**: conceptualisation; methodology; data collection. **Raquel Gonzalez-Perez**: methodology; data collection. **Isis O. Sosa-Sanchez**: writing the original draft. **Maria Isabel Peralta-Ramirez**: funding acquisition; conceptualisation; review and editing the manuscript; supervision.

ACKNOWLEDGEMENTS

Thank you to every pregnant woman and her babies who participated in the study. This study is a part of the Doctoral Thesis of Mr. Jose A. Puertas-Gonzalez. This work was supported by the Spanish Ministry of Science, Innovation and Universities (Project No. PID2019-110115GB-I00/SRA (State Research Agency)/10.13039/501100011033). Besides, Mr. Jose A. Puertas-Gonzalez has been awarded with an individual research grant (Spanish Ministry of Science, Innovation and Universities, FPU program, reference number 18/00617).

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Puertas-Gonzalez, J. A., Romero-Gonzalez, B., Mariño-Narvaez, C., Gonzalez-Perez, R., Sosa-Sanchez, I. O., & Peralta-Ramirez, M. I. (2023). Can we influence the neurological development and hair cortisol concentration of offspring by reducing the stress of the mother during pregnancy? A randomized controlled trial. *Stress and Health*, 1–13. https://doi.org/10.1002/smi.3222