Archives of Gynecology and Obstetrics (2022) 305:1421–1429
https://doi.org/10.1007/s00404-021-06251-z

MATERNAL-FETAL MEDICINE

Cumulative life stressors and stress response to threatened preterm labour as birth date predictors

Laura Campos-Berga[1] · Alba Moreno-Giménez[1] · Máximo Vento[1] · Vicente Diago[2] · David Hervás[3,4] · Pilar Sáenz[1] · Consuelo Cháfer-Pericás[1] · Ana García-Blanco[1,5]

Received: 22 April 2021 / Accepted: 1 September 2021 / Published online: 21 September 2021

Abstract

Purpose Preterm birth represents one of the main causes of neonatal morbimortality and a risk factor for neurodevelopmental disorders. Appropriate predictive methods for preterm birth outcome, which consequently would facilitate prevention programs, are needed. We aim to predict birth date in women with a threatened preterm labour (TPL) based on stress response to TPL diagnosis, cumulative life stressors, and relevant obstetric variables.

Methods A prospective cohort of 157 pregnant women with TPL diagnosis between 24 and 31 weeks gestation formed the study sample. To estimate the stress response to TPL, maternal salivary cortisol, α-amylase levels, along with anxiety and depression symptoms were measured. To determine cumulative life stressors, previous traumas, social support, and family functioning were registered. Then, linear regression models were used to examine the effect of potential predictors of birth date.

Results Lower family adaptation, higher Body Mass Index (BMI), higher cortisol levels and TPL diagnosis week were the main predictors of birth date. Gestational week at TPL diagnosis showed a non-linear interaction with cortisol levels: TPL women with middle- and high-cortisol levels before 29 weeks of gestation went into imminent labour.

Conclusion A combination of stress response to TPL diagnosis (salivary cortisol) and cumulative life stressors (family adaptation) together with obstetric factors (TPL gestational week and BMI) was the best birth date predictor. Therefore, a psychosocial therapeutic intervention program aimed to increase family adaptation and decrease cortisol levels at TPL diagnosis as well as losing weight, may prevent preterm birth in symptomatic women.

Keywords Cortisol · Previous traumas · Family functioning · Anxiety · Depressive symptoms · Preterm birth

Introduction

Despite advances in increasing infants' survival rate, preterm birth is still the main cause of neonatal morbidity [1] and represents one of the most leading risk factors for later neurodevelopmental disabilities during childhood [2]. Critically, the lack of accurate prediction methods of preterm birth in TPL women is a matter of concern due to the potential iatrogenic effects of repeated antenatal corticosteroid on the future child's neurodevelopment [3, 4], stressful and unnecessary hospitalizations, and elevated costs for public health system [5, 6]. One-third of pregnant women admitted to hospital suffer from a threatened preterm labour (TPL), but more than 50% do not progress to active labour [7] and only about half of preterm births cases are preceded by an identifiable risk factor [8]. Different prevention programs have been implemented around the world aimed to reduce

✉ Ana García-Blanco
ana.garcia-blanco@uv.es

1 Neonatal Research Unit, Health Research Institute La Fe, Av Fernando Abril Martorell, 106, 46026 Valencia, Spain

2 Division of Obstetrics and Gynecology, University and Polytechnic Hospital La Fe, Valencia, Spain

3 Data Science Unit, Biostatistics, and Bioinformatics, Health Research Institute La Fe, Valencia, Spain

4 Polytechnic University of Valencia, Valencia, Spain

5 Department of Personality, Evaluation, and Psychological Treatment, University of Valencia, Valencia, Spain

preterm birth [9] and social determinants are gaining consideration from renowned scientific organizations [10]. Therefore, reliable methods that allow physicians to stratify TPL women into low- and high-risk groups for preterm birth outcome are required.

A growing body of research indicates that both chronic life stress prior to conception and stressful events during pregnancy may act as potential risk factors for preterm birth [11, 12]. When personal coping strategies are saturated due to chronic life stress, overexposure to neuroendocrine mediators (e.g., cortisol or α-amylase) that maintain the homeostasis of Hypothalamic–Pituitary–Adrenal (HPA) axis [13, 14] and the Sympathetic–Adrenal–Medullary (SAM) axis [14], may have a deleterious impact on both mother and foetus [15], increasing the probability of preterm birth. Among possible causes of chronic stress, a history of traumatic events and poor social support or family functioning have usually been identified. In fact, it is well documented that a history of traumatic life events prior to conception may increase the risk of preterm birth [16–20]. However, although social support may modulate the association between life stressful events and preterm birth, findings are inconclusive [12, 21–23]. Whereas a systematic review concluded null relationship between maternal social support and preterm birth [22], more recent studies pointed out that specifically lack of partner support rather than global social support was associated with higher risk of preterm birth [21, 23, 24].

Regarding stressful events during pregnancy, they may alter normal balance of immune mediators, hormones, and neurotransmitters involved in timing of birth, increasing the risk of preterm birth [25, 26] as well as psychomotor impairments in infants [27]. Noteworthy, TPL is considered a stressful prenatal event likely to trigger a biopsychological stress response [28, 29]. First, from a biological perspective, a TPL event may dysregulate both the HPA axis [13, 14] and the SAM axis [14]. As for HPA axis biomarkers, research has revealed that cortisol levels at TPL diagnosis may predict birth 48 h after TPL diagnosis [30]. Conversely, other study addressing SAM activity measured by α-amylase levels showed inconclusive findings [14]. Whereas α-amylase dysregulation has been suggested as the underlying mechanism for the link between maternal depression and prematurity [31], no association between α-amylase levels and preterm birth has been found in non-depressed pregnant women [28, 29]. Second, from a psychological perspective, both gestational anxiety [32, 33] and depressive symptoms [34–36] which may be triggered by TPL diagnosis [37] can also be associated with preterm birth. In sum, women experiencing chronic life stress may need only another significant stressor during pregnancy such as TPL to reach the tipping point that leads to a preterm birth [32].

Even with the previous focused research efforts, it is still unclear which stress-related factors are most strongly associated with preterm birth, for several reasons mentioned below. First, although the impact of a stressful event during pregnancy can be modulated by a combination of biopsychosocial stress-related pathways (HPA or SAM stress biomarkers, anxious-depressive symptoms at TPL diagnosis, and/or previous traumatic events as well as social support), most studies have considered these factors separately [38]. Second, there seems to be a non-direct correlation between stress biomarkers determination and self-reported psychosocial stress by pregnant women [39]. Moreover, the few studies that have simultaneously examined different maternal stress-related variables also included non-TPL women and reported inconclusive findings: whereas some studies not using self-reports measures found an association between preterm birth and stress biomarkers [40, 41], others found that maternal self-reports may improve the biomarkers prediction [42]. Third, prospective studies with symptomatic women usually conduct only a 48 h follow-up after TPL diagnosis instead of until birth [30]. In the present follow-up study, multiple stress-related outcomes are studied simultaneously in symptomatic women from TPL diagnosis to birth date.

This study aims to predict birth date in women who suffered from a TPL by means of a combination of multiple stress-related factors: (i) cumulated life stressors (previous traumas, social support, and family functioning); and (ii) biopsychological response to TPL diagnosis (salivary cortisol and α-amylase as well as anxiety and depression symptoms). We expect that, considering studies that examine a combination of stress-related variables, biomarkers would be the strongest birth date predictors [40, 41]. However, self-reports assessing chronic social stress and acute psychological stress response to TPL diagnosis may improve this prediction model [42]. In addition, we expect that the association between stress biomarkers and self-reports might not be linear [39].

Materials and methods

This is a prospective cohort study performed in the Division of Obstetrics at a tertiary referral hospital during a 12-month period. The Ethics Committee at the Health Research Institute approved the study protocol (ref. 2015/0086), and informed consent was obtained from all participants.

Participants

Eligible participants were pregnant women diagnosed with/TPL between 24 and 31 + 6 weeks of gestation to guarantee that all participants were subjected to the same protocol treatment. TPL was diagnosed according to the following clinical criteria: regular uterine contractions associated with

cervical changes (≥ 80% cervical effacement or cervical dilation ≥ 2 cm), measured by the cervical ultrasound (cervical length < 25 mm). After TPL diagnosis, fetal cardiac activity and uterine contractions were monitored by abdominal ultrasound. If contractions persisted, women were admitted to the obstetric ward [43]. All women received one corticosteroids dose at least 12 h before saliva sample collection, and the second corticosteroids dose was administered after it. Considering that corticosteroid average lifetime is 12 h, antenatal steroid levels had already decreased notably when saliva sample was collected. Tocolytic therapy was atosiban or nifedipine [44]. Atosiban was initiated with a 6.75 mg/min bolus; then, a loading dose of 300 μg/min^{-1} for 3 h and a 48 h maintenance dose of 100 μg/min^{-1} were administered. Alternatively, nifedipine 20 mg, followed by 10 mg for each 20 min until 40 mg for 1 h, was administered [45]. Thus, all women received atosiban or nifedipine for less than 24 h as a whole. Finally, in cases of imminent labour (when cervix is between 4 and 10 cm dilated, rate of cervical dilation at least 1 cm/hour, effacement is usually complete, and fetal descent through birth canal begins), magnesium sulphate is usually administered but, in our sample, none of the participants received it before saliva collection.

Exclusion criteria involved severe medical conditions (e.g., diabetes mellitus), severe obstetric complications (placenta abruption, preeclampsia, intrauterine growth restriction, cervical dilation > 4 cm, infection, obstructed labour), fetal anomalies, teratogenic substances use, and social exclusion risk, which is considered a stressful condition that may act as confusing variable. To assess social exclusion risk, multidimensional criteria were employed: (i) risk of poverty; (ii) severe material deprivation; and/or (iii) jobless household [46]. A final sample of 151 TPL women completed the follow-up until birth. See Fig. 1 for the recruitment flow diagram.

Instruments and procedure

Psychological assessment

The following questionnaires were completed by participants in a 1 h session following recruitment.

- The Traumatic Experience Questionnaire (TEQ) [47, 48] is a screening test useful to detect post-traumatic stress disorder (PTSD). The questionnaire contains three parts evaluating: (i) a list of 19 potential traumatic events experienced; (ii) the most important traumatic event (qualitative dimension); and (iii) a list of 18 psychological symptoms according to DSM-IV criteria for PTDS whose sum represents the total score. The internal consistency coefficient for the symptoms scale was 0.88.
- The Multidimensional Scale of Perceived Social Support (MSPSS) [49] assesses individual's social support perception from 3 specific sources: family, friends, and significant person or partner. It is composed of 12 items rated on a 7-point Likert scale, and its internal consistency was 0.85 for the whole scale.
- The Family Adaptability Cohesion Evaluation Scale III (FACES III) [50] measures family Cohesion (degree to

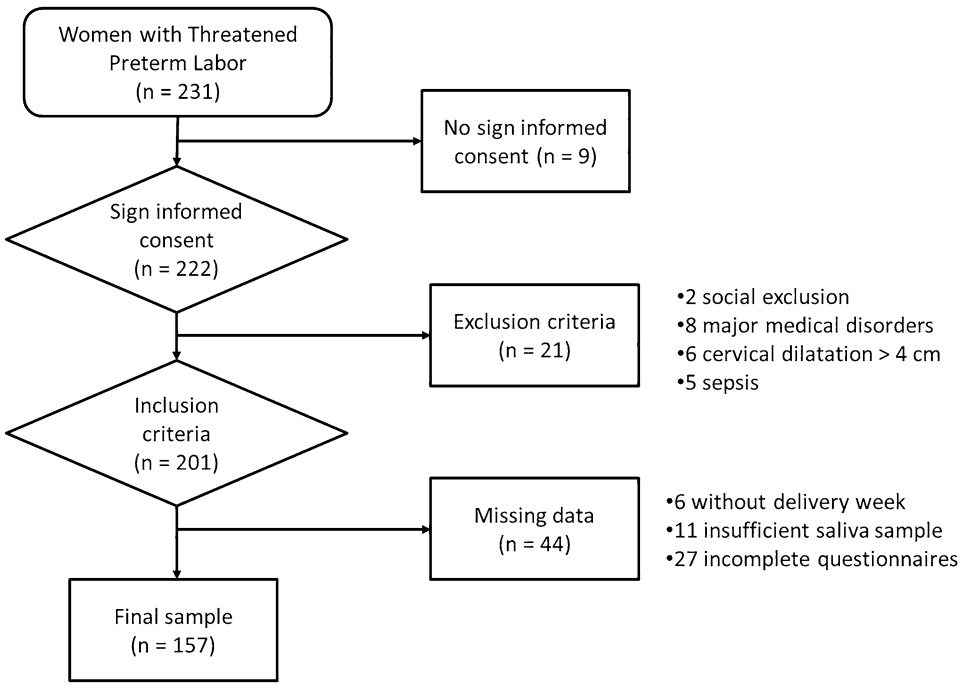

Fig. 1 Flow diagram describing the recruitment process, the exclusion determinants, and the participants who completed the study

which family members are separated from or connected to their family) and family Adaptability (extent to which the family system is flexible and able to change facing new circumstances). The test contains a total of 20 items rated on a 5-point scale according to the perceived frequency of different family living situations. It showed high internal consistency for Adaptability (0.87), Cohesion (0.86) and the total FACES scale (0.93).

- The State-Trait Anxiety Inventory (STAI) [51] was used to assess maternal trait and current state anxiety. It can be used in clinical settings to diagnose anxiety and to distinguish it from depressive syndromes. Each subscale is formed of 20 items rated on a 4-point scale, with higher scores indicating greater anxiety levels. Internal consistency coefficient for STAI-State scale was 0.89.
- The Beck Depression Inventory Short Form (BDI/SF) [52] measures typical depressive attitudes and symptoms in both psychiatric and non-psychiatric populations. It contains 13 items rated on a 4-point Likert scale, where scores ≥ 5 points suggest probable depression (5–7 mild, 8–15 moderate, > 15 severe). Internal consistency was 0.73.

Stress biomarkers

Concerning analytical determinations, standard of cortisol was purchased from Sigma-Aldrich Química SA (Madrid, Spain). Saliva samples were collected in the morning after admission between 10 and 12 a.m. (minimum 1 h after breakfast). Samples were stored at − 80 °C and were thawed on ice and homogenized. The sample treatment to determine cortisol was based on previous work [53]. Briefly, 25 µL of sample were subjected to liquid–liquid extraction to extract cortisol, then the organic layer was evaporated to dryness and the residues were reconstituted in water (pH 3): methanol (85:15 v/v) solution. Finally, 5 µL were injected in the chromatographic system (ultra-performance liquid chromatography coupled to tandem mass spectrometry).

Salivary α-amylase assay kit was acquired from Salimetrics (Suffolk, United Kingdom). For the α-amylase determination, samples were vortexed and centrifuged. Then, they were diluted with the α-amylase diluent at 1:200 as final dilution. Finally, they were subjected to the kinetic enzyme assay.

Statistical analysis

As for statistical analysis, data were summarized using mean (standard deviation) and median (1st, 3rd quartile) for continuous variables and relative and absolute frequencies for categorical variables. Correlations among stress-related variables were assessed with Spearman's correlation. Association between potential birth predictors and final birth date (weeks) was assessed using a linear regression model. Parity, Body Mass Index (BMI), multiple pregnancy, in-vitro fertilization, and the gestational week at TPL diagnosis were also included due to their potential influence on preterm birth [53]. Selection of the predictors included in the model was performed using L1 penalization. The lambda parameter was selected using 500 repetitions of tenfold cross-validation. Model performance was assessed estimating optimism corrected R-square using bootstrapping [54]. All statistical analyses were performed using R (version 3.5.3), rms (version 5.1–3.1) and glmnet (version 2.0–16).

Results

Socio-demographic and clinical variables of the sample are summarized in Table 1. Prior to modelling, an exploratory data analysis was performed by examining correlations between the different stress-related variables (see Fig. 2). Chronic stress-related variables showed moderate to strong correlations among them (MSPSS and FACES). Similarly, acute psychological stress-related responses to TPL (STAI and BDI) moderately correlated to each other. No other evident associations were found.

Variable selection using L1 penalization specified four predictors as the optimum complexity for the linear regression predictive model (Table 2). These variables were family adaptation (FACES), maternal BMI, TPL gestational week, and cortisol levels. Additionally, a non-linear trend for TPL week using regression splines was added to the model.

$$\begin{aligned}\text{Birth Week} = {} & -43.49 - 0.23*\text{BMI} + 2.92*\text{TPLweek} - 0.04*\max(\text{TPLweek} - 24, 0)^3 + 0.21*\max(\text{TPLweek} - 29, 0)^3 - 0.26*\max(\text{TPLweek} - 31, 0)^3 + 0.009*\max(\text{TPLweek} - 33, 0)^3 - 18.21*\log(\text{cortisol}) + 0.11*\text{adaptation} + \log(\text{cortisol})*(0.66*\text{TPLweek} - 0.009*\max(\text{TPLweek} - 24, 0)^3 + 0.06*\max(\text{TPLweek} - 29, 0)^3 - 0.08*\max(\text{TPLweek} - 31, 0)^3 + 0.03*\max(\text{TPLweek} - 33, 0)^3.\end{aligned}$$

This model had an *R*-squared value of 0.37 and an optimism corrected *R*-squared value of 0.30. To aid in the interpretation of the non-linear effect of TPL week, a marginal effects plot for this variable and its interaction with log (cortisol) values is provided (Fig. 3).

Discussion

Main findings

This study highlights the relevance of considering a combination of multiple stress-related variables, that is: (i)

Table 1 Socio-demographic and clinical variables of the final sample

Variable	Final sample ($n = 157$)
	Mean (SD)/*n*(%)
	Median (1st, 3rd Q.)
Maternal age	31.75 (5.41)
	32 (28, 36)
Parity	0.52 (0.92)
	0 (0, 1)
BMI	22.58 (3.07)
	22.04 (21, 23)
Threatened preterm labour week	29.57 (2.87)
	30 (28, 32)
State STAI	20.01 (9.72)
	18 (14, 24)
Trait STAIR	17.86 (8.76)
	17 (11, 22)
BDI–II	3.01 (3.11)
	2 (1, 4)
Friends MSPSS	25.18 (3.61)
	27 (24, 28)
Family MSPSS	26.43 (2.6)
	28 (26, 28)
Partner MSPSS	27.1 (1.91)
	28 (27, 28)
Adaptation FACES III	30.53 (6.42)
	30 (28, 34)
Cohesion FACES III	31.73 (5.32)
	32 (29, 35)
TEQ	2.91 (4.26)
	0 (0, 5)
Cortisol (nmol L^{-1})	3.06 (4.95)
	1.33 (0.05, 3.61)
α-amylase (U mL^{-1})	68.18 (65.42)
	54.12 (27.95, 78.92)
In-vitro fertilization	
No	141 (89.81%)
Yes	16 (10.19%)
Multiple pregnancy	
No	89 (56.69%)
Yes	68 (43.31%)

BMI Body Mass Index, *STAI* State-Trait Anxiety Inventory, *BDI/SF* Beck depression inventory short form, *MSPSS* multidimensional scale of perceived social support, *FACES* family adaptability cohesion evaluation scale, *TEQ* Traumatic Experience Questionnaire

cumulated life stressors (previous traumas, social support, and family functioning); and (ii) the biopsychological response to TPL diagnosis (salivary cortisol and α-amylase as well as anxiety and depression symptoms) when attempting to predict birth date in TPL women. According to previous research [39], the relationship between self-reported stress tests and biomarkers levels seems to be weak in TPL women. Focusing on stress measures most strongly associated with our study outcome, lower family adaptation, higher BMI, and middle and high levels of cortisol in women with TPL diagnosis before 29 weeks of gestation were the best predictors of preterm birth. Thus, given multifactorial aetiology of stress [38], taking all these elements together and performing simultaneous analysis of both psychosocial (family adaptation) and biological variables (cortisol levels) as well as obstetric factors (BMI and the TPL diagnosis week) improves birth date prediction better than analysing these factors separately [42].

Strengths and limitations

The strengths of this study are as follows: (i) the inclusion of multiple stress-related variables; (ii) the successful follow-up of participants from TPL diagnosis to birth; (iii) the rigorous inclusion criteria to control for additional stressful variables such as social exclusion or major medical illness; and (iv) the consideration of other potential obstetric predictors such as BMI, TPL diagnosis week, multiple pregnancy, in vitro fertilization, or parity in the regression model. In turn, these strengths have limited generalizability of results and sample size. Furthermore, participants were not included if any data were missing or the follow-up was not completed, which could cause a selection bias. Finally, although all pregnant women at 24–31 + 6 weeks received similar treatment, individual differences in response to tocolytic agents and corticosteroids could have influenced biomarkers determinations.

Clinical interpretation

Regarding stress biomarkers, middle- and high-cortisol levels in women with TPL diagnosis before 29 weeks of gestation predicted earlier birth date. In line with Campbell et al. (2005) [30], increasing levels of HPA axis biomarkers were relevant for determining birth date in TPL women. However, whereas they observed that stress biomarkers had a significant association with prematurity from the 28th week of gestation and onwards [30], our findings have shown this association from the 24th to 29th weeks of gestation. This discrepancy may be explained due to differences in the follow-up length; whereas Campbell et al. (2005) [30] carried out a 48 h follow-up after TPL diagnosis, our research extended it until birth time. With regard to α-amylase levels, no differences have been observed, indicating that α-amylase biomarker is not a significant variable to predict birth week in symptomatic women (see García-Blanco et al. (2017) for a similar finding) [28, 29]. In this case, previous research reporting an association between α-amylase levels

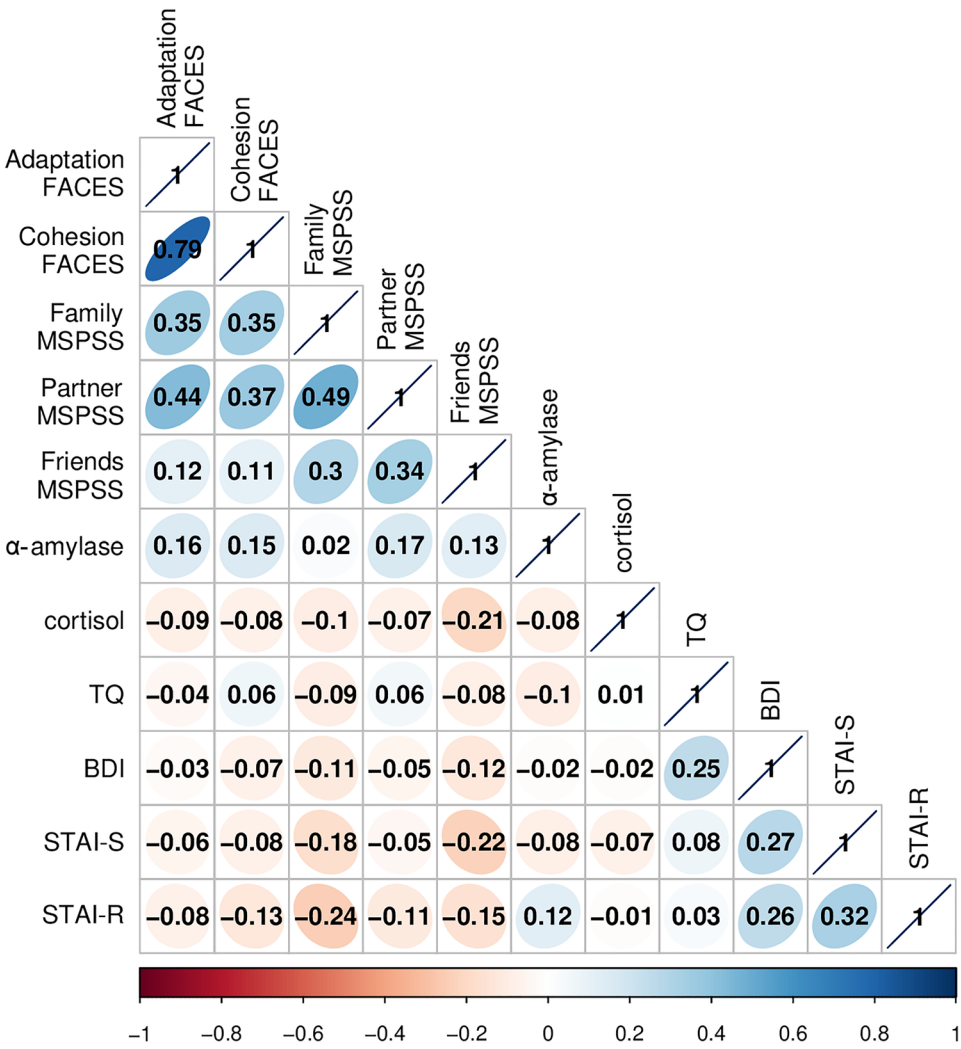

Fig. 2 Correlation plot between the different stress-related variables

Table 2 Results of the fitted linear regression model to predict the birth week

Variable	Coefficient	95% CI	*p* value
(Intercept)	− 43.49	[− 70.3, − 16.7]	0.002
Adaptation FACES III	0.11	[0.026, 0.19]	0.01
BMI	− 0.23	[− 0.41, − 0.05]	0.012
log(cortisol)	− 18.21	[− 28.9, − 7.54]	0.001
TPLweek	2.92	[1.91, 3.92]	< 0.001
TPLweek’	− 3.04	[− 4.53, − 1.55]	< 0.001
TPLweek’’	17.27	[6.43, 28.1]	0.002
TPLweek:log(cortisol)	0.66	[0.25, 1.07]	0.002
TPLweek’:log(cortisol)	− 0.75	[− 1.38, − 0.11]	0.022
TPLweek’’:log(cortisol)	4.91	[0.19, 9.63]	0.041

BMI Body Mass Index, *FACES* family adaptability cohesion evaluation scale, *TPL* threatened preterm labour

and preterm birth suggested that this relationship may be restricted to women with prenatal depression [31].

As for psychological response to TPL, unlike previous studies that found an association between preterm birth and gestational anxiety [32, 33] and depressive symptoms [34–36], maternal self-reported symptoms after a TPL were not relevant to estimate birth week in our sample. Thus, this apparent inconsistency may be attributable to the inclusion of women without TPL in previous research. Undoubtedly, all women with a TPL diagnosis were expected to react with a subjective increase of anxiety and depressive symptoms. Nevertheless, only some of those women have shown middle- and high-cortisol levels. Therefore, this study has shown that stress biomarkers were stronger predictors than the subjective state anxiety for TPL women. Like it occurs with anxiety symptoms, suffering traumatic experiences previously to pregnancy may be associated with preterm birth in asymptomatic women [17, 19, 20]. However, such differences have not been observed in this study with symptomatic women.

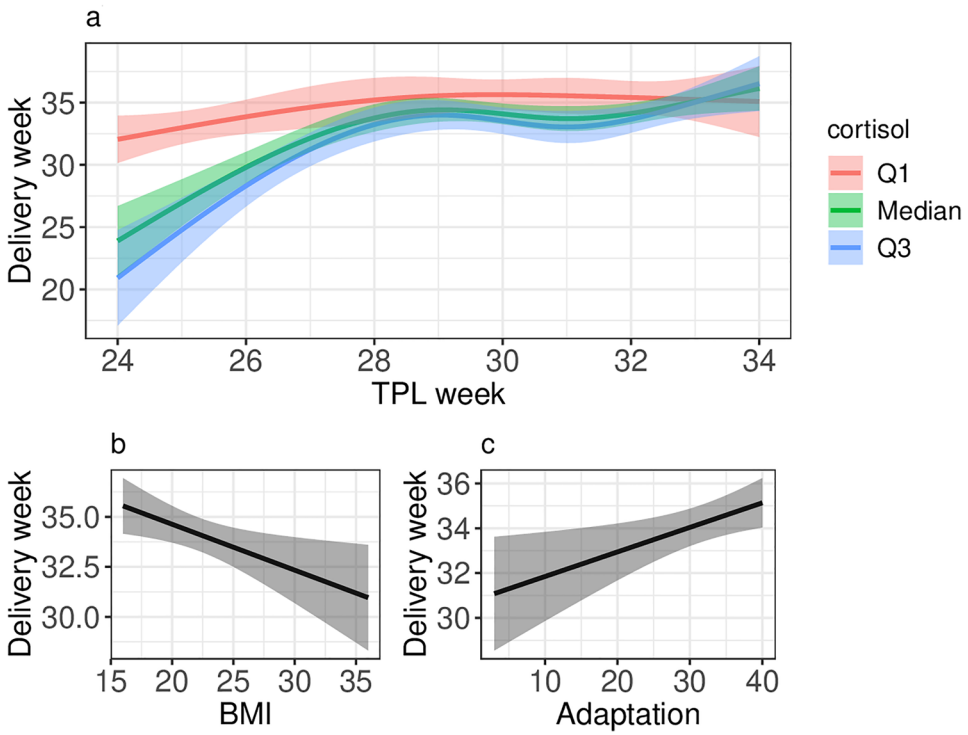

Fig. 3 Marginal effect plots depicting the relationship between labour week and **a** log(cortisol) interaction with TPL week, **b** Body Max Index, and **c** family adaptation

It could be expected that previous traumas are not as relevant in this context, because TPL represents a traumatic event itself. Hence, TPL can be considered as a pregnancy-specific traumatic event that may provoke a stress-vulnerability status in all cases [16].

Concerning chronic social stress-related variables, family adaptation was a relevant factor to estimate the final birth date. Likewise, other studies with non-TPL women have concluded that some aspects of family functioning (e.g., poor emotional understanding by the partner) are related to preterm birth [21, 23]. In our study, family's ability to modify its rules, roles, and structure in response to environmental changes, rather than social support in general [22], was the most relevant social factor predictor [21, 23]. Therefore, among psychosocial self-reported measures, chronic social stress—represented by family adaptation difficulties—seems to be a stronger predictor for preterm birth than maternal anxious-depressive symptoms after a TPL diagnosis. Thus, although TPL can trigger an increase of subjective anxiety in all women, stable family functioning, on the contrary, may act as a modulator compensating potential deleterious effect of TPL and consequently reducing risk of preterm birth.

Finally, relating to obstetric variables, according to prior literature about preterm birth [54], actors such as maternal BMI and gestational week at TPL diagnosis have also been relevant predictors for final birth date in our study.

Conclusion

This follow-up study uses a multidimensional approach to examine stress response in pregnant women with an antenatal adverse event such as TPL to explore potential indicators of vulnerability to preterm birth. These findings can be applied as a new useful tool to determine final birth date in TPL women by means of a simultaneous analysis of chronic social stressors (family adaptation) and biological stress response to TPL diagnosis (salivary cortisol) together with obstetric conditions (BMI and gestational week). This study has important public health implications, since the number of preterm births may be reduced by initiating early preventive psychosocial interventions to increase family adaptation and decrease cortisol levels after a TPL as well as lose weight in symptomatic women.

Acknowledgements We are greatly indebted to all the pregnant women, their families, nursing, and medical staff who voluntarily participated in the present study. Without their collaboration and enthusiasm, this study could not have been completed.

Author contributions MV: protocol/project development; funding acquisition; supervision; manuscript writing/editing. AM-G: data collection; manuscript writing/editing. LC-B: data collection; manuscript writing/editing. VD: protocol/project development; funding acquisition; supervision; manuscript writing/editing. DH: data analysis; software; manuscript writing. PS: protocol/project development; data collection; manuscript writing/editing. CC: protocol/project development; data analysis; manuscript writing/editing. AG-B: protocol/project

development; funding acquisition; data collection; supervision; manuscript writing/editing.

Funding Prior to study initiation, a grant was awarded by the Instituto de Salud Carlos III (PI18/01352). To achieve this grant, the project was assessed by an external peer review panel, guaranteeing scientific quality and ethical integrity. MV acknowledges PI17/0131 grant from the Instituto de Salud Carlos III (Spanish Ministry of Economy and Competitiveness) (ISCIII; Plan Estatal de I + D + I 2013–2016) and co-financed by the European Development Regional Fund "A way to achieve Europe" (ERDF); and RETICS funded by the PN 2018–2011 (Spain), ISCIII- Sub-Directorate General for Research Assessment and Promotion and the European Regional Development Fund (FEDER), RD16/0022/0001.VD acknowledges PI18/01352 grant from the ISCIII. CC-P acknowledges a "Miguel Servet I" grant (CP16/00082) from the ISCIII. AG-B acknowledges a "Juan Rodés" grant (JR17/00003) and a health research project (PI18/01352) from the ISCIII. LC-B acknowledges a "Río Hortega" grant (CM20/00143) from the ISCIII.

Availability of data and material Collected data and materials of assessment comply with field standards and are available if required.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethics approval The Ethics Committee at the La Fe Health Research Institute approved the study protocol in 2015 (ref. 2015/0086) and informed consent was obtained from all participants.

References

1. Vogel JP, Chawanpaiboon S, Moller AB, Watananirun K, Bonet M, Lumbiganon P (2018) The global epidemiology of preterm birth. Best Pract Res Clin Obstet Gynaecol 52:3–12. https://doi.org/10.1016/j.bpobgyn.2018.04.003
2. Luu TM, Mian MOR, Nuyt AM (2017) Long-term impact of preterm birth: neurodevelopmental and physical health outcomes. Clin Perinatol 44(2):305–314. https://doi.org/10.1016/j.clp.2017.01.003
3. Jobe AH (2019) Neonatal stress and resilience—lasting effects of antenatal corticosteroids. Can J Physiol Pharmacol 97(3):155–157. https://doi.org/10.1139/cjpp-2018-0240
4. Roberts D, Brown J, Medley N, Dalziel SR (2017) Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD004454.pub3
5. Garcia-Casado J, Ye-Lin Y, Prats-Boluda G, Mas-Cabo J, Alberola-Rubio J, Perales A (2018) A Electrohysterography in the diagnosis of preterm birth: a review. Psysiol Measur. https://doi.org/10.1088/1361-6579/aaad56
6. Di Renzo GC, Roura LC, Facchinetti F, Helmer H, Hubinont C, Jørgensen JS et al (2017) Preterm labor and birth management: recommendations from the european association of perinatal medicine preterm labor and birth management. J Matern Fetal Neonatal Med 30(17):2011–2030. https://doi.org/10.1080/14767058.2017.1323860
7. Gazmararian JA, Petersen R, Jamieson DJ, Schild L, Adams MM, Deshpande AD, Franks AL (2002) Hospitalizations during pregnancy among managed care enrollees. Am Coll Obstet Gynecol 100(1):94–100. https://doi.org/10.1016/s0029-7844(02)02024-0
8. Glover AV, Manuck TA (2018) Seminars in fetal & neonatal medicine screening for spontaneous preterm birth and resultant therapies to reduce neonatal morbidity and mortality: a review. Semin Fetal Neonatal Med 23(2):126–132. https://doi.org/10.1016/j.siny.2017.11.007
9. Vitner D, Barrett J, Katherine W, White SW, Newnham JP (2020) Community-based, population-focused preterm birth prevention programs—a review. Arch Gynecol Obstet 302(6):1317–1328. https://doi.org/10.1007/s00404-020-05759-0
10. American College of Obstetricians and Gynecologists (2018) ACOG committee opinion No. 729: importance of social determinants of health and cultural awareness in the delivery of reproductive health care. Obstet Gynecol 131(6):1162–1163. https://doi.org/10.1097/AOG.0000000000002660
11. Olson DM, Severson EM, Verstraeten BSE, Ng JWY, Mccreary JK, Metz GAS (2015) Allostatic load and preterm birth. Int J Mol Sci. https://doi.org/10.3390/ijms161226209
12. Weber KA, Carmichael SL, Yang W, Tinker SC, Shaw GM (2020) Periconceptional stressors and social support and risk for adverse birth outcomes. BMC Pregnancy Childbirth 20(1):487. https://doi.org/10.1186/s12884-020-03182-6
13. Guardino CM, Schetter CD, Saxbe DE, Adam EK, Ramey SL, Shalowitz MU, Community Child Health Network (CCHN) (2017) Diurnal salivary cortisol patterns prior to pregnancy predict infant birth weight. Physiol Behav 176(12):139–148. https://doi.org/10.1016/j.physbeh.2017.03.040
14. Shapiro GD, Fraser WD, Frasch MG, Séguin JR (2013) Psychosocial stress in pregnancy and preterm birth: associations and mechanisms. J Perinat Med 41(6):631–645. https://doi.org/10.1515/jpm-2012-0295
15. Lupien SJ, Juster RP, Raymond C, Marin MF (2018) The effects of chronic stress on the human brain: From neurotoxicity, to vulnerability, to opportunity. Front Neuroendocrinol 49:91–105. https://doi.org/10.1016/j.yfrne.2018.02.001
16. Ghosn F, Almansa B, Moreno-Giménez A, Sahuquillo-Leal R, Serrano-Lozano E, Hervás D, Diago V, Cháfer-Pericás C, Vento M, García Blanco A (2019) Trajectories of stress biomarkers and anxious- depressive symptoms from pregnancy to postpartum period in women with a trauma history. Eur J Psychotraumatol. https://doi.org/10.1080/20008198.2019.1601990
17. Khashan AS, Mcnamee R, Abel KM, Mortensen PB, Kenny LC, Pedersen MG et al (2009) Rates of preterm birth following antenatal maternal exposure to severe life events: a population-based cohort study. Reprod Epidemiol 24(2):429–437. https://doi.org/10.1093/humrep/den418
18. Liou SR, Wang P, Cheng CY (2016) Effects of prenatal maternal mental distress on birth outcomes. Women Birth 29(4):376–380. https://doi.org/10.1016/j.wombi.2016.03.004
19. Nesari M, Olson JK, Vandermeer B, Slater L, Olson DM (2018) Does a maternal history of abuse before pregnancy affect pregnancy outcomes? A systematic review with meta-analysis. BMC Pregnancy Childbirth 18(1):1–11. https://doi.org/10.1186/s12884-018-2030-8
20. Witt WP, Cheng ER, Wisk LE, Litzelman K, Chatterjee D, Mandell K (2014) Preterm birth in the United States: the impact of stressful life events prior to conception and maternal age. Am J Public Health 104:73–80. https://doi.org/10.2105/AJPH.2013.301688
21. Hetherington E, Doktorchik C, Premji SS, Mcdonald SW, Tough SC, Sauve S (2015) Preterm birth and social support during pregnancy: a systematic review and meta-analysis. Pediatr Perinatal Epidemiol 29:523–535. https://doi.org/10.1111/ppe.12225
22. Orr ST (2004) Social support and pregnancy outcome: a review of the literature. Clin Obstet Gynecol 47(4):842–855. https://doi.org/10.1097/01.grf.0000141451.68933.9f

23. Rauchfuss M, Maier B (2011) Biopsychosocial predictors of preterm delivery. J Perinat Med 39:515–521. https://doi.org/10.1515/JPM.2011.067
24. Surkan PJ, Dong L, Ji Y, Hong X, Ji H, Kimmel M, Tang WY, Wang X (2019) Paternal involvement and support and risk of preterm birth: findings from the Boston birth cohort. J Psychosom Obstet Gynecol 40(1):48–56. https://doi.org/10.1080/0167482X.2017.1398725
25. Arck PC (2001) Stress and pregnancy loss: role of immune mediators, hormones and neurotransmitters. Am J Reprod Immunol 46:117–123. https://doi.org/10.1111/j.8755-8920.2001.460201.x
26. Braun K, Bock J, Wainstock T, Matas E, Gaisler-salomon I, Fegert J et al (2017) Neuroscience and biobehavioral reviews experience-induced transgenerational (re-) programming of neuronal structure and functions: Impact of stress prior and during pregnancy. Neurosci Biobehav Rev. https://doi.org/10.1016/j.neubiorev.2017.05.021
27. Polanska K, Krol A, Merecz-Kot D, Jurewicz J, Makowiec-Dabrowska T, Chiarotti F, Hanke W (2017) Maternal stress during pregnancy and neurodevelopmental outcomes of children during the first 2 years of life. J Paediatr Child Health 53(3):263–270. https://doi.org/10.1111/jpc.13422
28. García-Blanco A, Diago V, Serrano V, Cruz DL, Hervás D (2017) Can stress biomarkers predict preterm birth in women with threatened preterm labor? Psychoneuroendocrinology 83:19–24. https://doi.org/10.1016/j.psyneuen.2017.05.021
29. García-Blanco A, Monferrer A, Grimaldos J, Hervás D, Balanzá-Martínez V, Diago V, Vento M, Cháfer-Pericás C (2017) A preliminary study to assess the impact of maternal age on stress-related variables in healthy nulliparous women. Psychoneuroendocrinology 78:97–104. https://doi.org/10.1016/j.psyneuen.2017.01.018
30. Campbell MK, Challis JRG, Dasilva O, Bocking AD (2005) A cohort study found that white blood cell count and endocrine markers predicted preterm birth in symptomatic women. J Clin Epidemiol 58:304–310. https://doi.org/10.1016/j.jclinepi.2004.06.015
31. Braithwaite EC, Ramchandani PG, Lane TA, Murphy SE (2015) Symptoms of prenatal depression are associated with raised salivary alpha-amylase levels. Psychoneuroendocrinology 60:163–172. https://doi.org/10.1016/j.psyneuen.2015.06.013
32. Ding X, Wu Y, Xu S, Zhu R, Jia X (2014) Maternal anxiety during pregnancy and adverse birth outcomes: a systematic review and meta-analysis of prospective cohort studies. Journal of Afective Disorders 159(81):103–110. https://doi.org/10.1016/j.jad.2014.02.027
33. Grigoriadis S, Graves L, Peer M, Mamisashvili L, Tomlinson G, Vigod SN et al (2018) Maternal anxiety during pregnancy and the association with adverse perinatal outcomes: systematic review and meta-analysis. J Clin Psychiatry. https://doi.org/10.4088/JCP.17r12011
34. Field T (2017) Prenatal depression risk factors, developmental effects and interventions: a review. J Pregnancy Child Health 04(01):1–25. https://doi.org/10.4172/2376-127x.1000301
35. Hermon N, Wainstock T, Sheiner E, Golan A, Walfisch A (2019) Impact of maternal depression on perinatal outcomes in hospitalized women—a prospective study. Arch Women's Mental Health. https://doi.org/10.1007/s00737-018-0883-5
36. Liu C, Cnattingius S, Bergström M, Östberg V, Hjern A (2016) Prenatal parental depression and preterm birth: a national cohort study. Int Jo Obstetr Gynaecol 123(12):1973–1982. https://doi.org/10.1111/1471-0528.13891
37. Dagklis T, Tsakiridis I, Chouliara F, Mamopoulos A, Rousso D, Athanasiadis A, Papazisis G (2018) Antenatal depression among women hospitalized due to threatened preterm labor in a high-risk pregnancy unit in Greece. J Maternal-Fetal Neonatal Med 31(7):919–925. https://doi.org/10.1080/14767058.2017.1301926
38. Field T, Diego M, Hernandez-reif M (2009) Prematurity and potential predictors. Int J Neurosci 118:277–298. https://doi.org/10.1080/00207450701239327
39. Himes KP, Simhan HN (2011) Plasma corticotropin-releasing hormone and cortisol concentrations and perceived stress among pregnant women with preterm and term birth. Am J Perinatol 1(212):443–448. https://doi.org/10.1055/s-0030-1270119
40. Hoffman MC, Mazzoni SE, Wagner BD, Laudenslager ML, Ross RG (2016) Measures of maternal stress and mood in relation to preterm birth. Obstet Gynecol 127(3):545–552. https://doi.org/10.1097/AOG.0000000000001287
41. Pearce BD, Grove J, Bonney EA, Bliwise N, Dudley DJ, Schendel DE, Thorsen P (2010) Interrelationship of cytokines, hypothalamic-pituitary-adrenal axis hormones, and psychosocial variables in the prediction of preterm birth. Gynecol Obstet Invest 70:40–46. https://doi.org/10.1159/000284949
42. Ruiz RJ, Fullerton J, Brown CEL, Dudley DJ (2002) Predicting risk of preterm birth: the roles of stress, clinical risk factors, and corticotropin. Biol Res Nurs 4:54–64. https://doi.org/10.1177/1099800402004001007
43. American College of Obstetricians and Gynecologists (2016) ACOG practice bulletin no. 171: Management of preterm labor. Obstetr Gynecol. https://doi.org/10.1097/AOG.0000000000001711
44. Ali AA, Sayed AK, Sherif E, Loutfi GO, Mahmoud A, Ahmed M et al (2019) Systematic review and meta-analysis of randomized controlled trials of atosiban versus nifedipine for inhibition of preterm labor. Int J Gynecol Obstectr 145:139–148. https://doi.org/10.1002/ijgo.12793
45. Conde-Agudelo A, Romero R, Kusanovic JP (2011) Nifedipine in the management of preterm labor: a systematic review and metaanalysis. Am J Obstetr 204(2):134.e1-134.e20. https://doi.org/10.1016/j.ajog.2010.11.038
46. Savova I (2012) Europe 2020 strategy-towards a smarter, greener and more inclusive EU economy? Eurostat (EU Commission). https://doi.org/10.2785/101636 (**ISSN 1977-0316**)
47. Davidson J, Smith R (1990) Traumatic experiences in psychiatric outpatients. J Trauma Stress 3(3):459–475
48. Bobes J, Calcedo-Barba A, García M, François M, Rico-Villademoros F, González MP, Bousoño M (2000) Evaluación de las propiedades psicométricas de la versión española de cinco cuestionarios para la evaluación del trastorno de estrés postraumático. Actas Esp Psiquiatr 28(4):207–218
49. Zimet GD, Dahlem NW, Zimet SG, Gordon K, Farley GK (1988) The multidimensional scale of perceived social support the multidimensional scale of perceived social support. J Pers Assess 52(1):37–41. https://doi.org/10.1207/s15327752jpa5201
50. Olsen DH, Portner J, Lavee Y (1985) Family adaptability and cohesion evaluation scales (FACES-II). University of Minnesota, Minneapolis
51. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA (1983) Manual for the state-trait anxiety inventory. CA, Consulting Psychologists Press, Palo Alto
52. Beck AT, Rial WY, Rickels K (1974) Short form of depression inventory: cross-validation. Psychol Rep 34:1184
53. García-Blanco A, Vento M, Diago V, Cháfer-Pericás C (2016) Reference ranges for cortisol and α-amylase in mother and newborn saliva samples at different perinatal and postnatal periods. J Chromatogr B Anal Technol Biomed Life Sci 1022:249–255. https://doi.org/10.1016/j.jchromb.2016.04.035
54. Goldenberg RL, Culhane JF, Iams JD, Romero R (2008) Preterm Birth 1 Epidemiology and causes of preterm birth. Lancet 371:75–84. https://doi.org/10.1016/S0140-6736(08)60074-4