Inflammatory markers of perinatal depression in women with and without history of trauma

Marker infiammatori di depressione perinatale in donne con e senza storia di trauma

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SUMMARY. Purpose. Increased inflammation has been described as consistently associated with depression. Moreover, the pro-inflammatory pattern was found in women with a history of trauma irrespective of major depression diagnosis. In this study, we explored the possible association of inflammatory markers with perinatal depression (PND), measuring serum levels of cytokines (IL-6, TNF-a, IFN-γ), acute phase proteins (CRP), erythrocyte sedimentation rate (ESR), cortisol and brain-derived neurotrophic factor (BDNF) in women at the second trimester of pregnancy. Moreover, we tested whether the biological markers were correlated with the severity of PND, trauma history and resilience level. **Methods.** Seventy-nine women including two groups of patients (women with PND at the second trimester of pregnancy with and without history of trauma) and two healthy control groups (inside and outside the peripartum) were enrolled. Blood sampling were collected for measuring putative biological markers. Clinical interview, Edinburgh Postnatal Depression Scale (EPDS), Inventory of Traumatic experiences (TEC), Connor–Davidson Resilience Scale (CD-RISC) were administered. **Results.** Women with PND and trauma reported a higher EPDS (p=0.004) and lower CD-RISC scores compared to other groups (F=34.77; p<0.001). The one-way ANOVA analysis showed lower ERS (F=2.87; p=0.040), CRP (F42=4.05; p=0.010) mean values among PND women without trauma and higher TNF-α mean values (F=6.07; p=0.001) among PND women with trauma history compared to other groups. **Conclusions.** History of trauma was associated with a more severe clinical phenotype of PND and decreased resilience level. The increase of acute phase proteins in women with PND and higher TNF-α level in those with trauma exposure validated the inflammatory theory of PND. Our findings substantiated the need of implementing the screening of pregnant women with the assessment of trauma history. Properly, resilience-enhancing interventions are recommended with the aim of support mothers and mitigate the possible transgenerational transmission of pathology. The biological results are compelling although preliminary.

KEY WORDS: affective disorders, cytokines, inflammation, perinatal depression, trauma, women health.

RIASSUNTO. Scopo. L'ipotesi infiammatoria della depressione è stata ampiamente descritta nella depressione maggiore con alcune evidenze anche per la depressione perinatale. La risposta allo stress presente in alcuni individui con depressione, espressa dall'attività dell'asse ipotalamo-ipofisi-surrene, potrebbe essere associata a un pattern neurobiologico pro-infiammatorio. Le citochine infiammatorie, IL-1, IL-6 e TNF-α, svolgono funzioni ancora più complesse intervenendo nei meccanismi di proliferazione e differenziazione delle cellule nervose, come dimostrato dall'azione sulla sintesi e l'attività del BDNF (fattore neurotrofico cerebrale). Inoltre, il profilo pro-infiammatorio sembra strettamente associato alla presenza di antecendenti traumatici indipendentemente dalla diagnosi di depressione. In questo studio abbiamo esplorato le possibili correlazioni tra citochine infiammatorie (IL-6, TNF-a, IFN-γ), indici di flogosi (PCR e VES), ormoni dello stress (cortisolo) e BDNF con la depressione perinatale. In particolare, abbiamo indagato l'associazione di questi markers con la severità dei sintomi depressivi, controllando anche il possibile effetto degli antecedenti traumatici e il ruolo protettivo della resilienza. **Metodi.** Abbiamo arruolato un campione totale di 79 donne diviso in quattro gruppi. I primi due gruppi sono formati da donne al secondo trimestre di gravidanza affette da depressione perinatale, con e senza antecedenti traumatici. I due gruppi di controllo includono donne in gravidanza e donne al di fuori del periodo perinatale. Sono stati raccolti campioni di sangue per la misurazione dei marker biologici. Ai due gruppi di pazienti sono stati somministrati un'intervista psichiatrica per la diagnosi di depressione perinatale e test psicometrici: Edinburgh Postnatal Depression Scale (EPDS), Inventory of Traumatic experiences (TEC), Connor-Davidson Resilience Scale (CD-RISC). **Risultati.** Le donne con depressione perinatale e storia di trauma avevano punteggi più alti della scala EPDS (p=0,004) e valori più bassi del test CD-RISC (F=34,77; p<0,001) rispetto agli altri gruppi. L'analisi one-way ANOVA ha mostrato differenze significative nei valori medi di VES (F=2,87; p=0,040) e di PCR (F42=4,05; p=0,010) nel gruppo di donne con depressione perinatale e trauma e di TNF-α (F=6,07; p=0,001) nelle donne con depressione perinatale senza antecedenti traumatici. **Conclusioni.** La storia di trauma è associata a fenotipi clinici di depressione perinatale più severi e ridotti livelli di resilienza. I nostri risultati preliminari sull'aumento delle proteine di fase acuta in donne affette da DPN e di un livello più alto di TNF-a nel campione di donne con depressione e storia di trauma e avvalorano l'ipotesi infiammatoria nella DPN. Lo screening per la depressione peri-

natale dovrebbe includere di routine la valutazione degli antecedenti traumatici che si associano a sintomi più severi di depressione. Interventi focalizzati sul trauma e sulla resilienza potrebbero avere il duplice ruolo di supportare le madri affette da depressione in gravidanza e mitigare la trasmissione transgenerazionale psicopatologica madre-bambino.

PAROLE CHIAVE: citochine, depressione, depressione perinatale, infiammazione, medicina di genere, trauma.

INTRODUCTION

The perinatal phase is conceived as a well-known trigger of psychiatric disorders[1] and perinatal depression (PND) is a disabling disorder that affects as many as one in five women[2].

The view of PND as a subtype of depression or as a distinct clinical entity, related to a women`s reproductive cycle is a subject of debate[3,4]. However, the influence of inflammation on the development of PND is a matter of investigation due to the well-established role of immune activation in major depression[5-7]. With regards to PND, inflammation may be involved in its development interplaying either with sex hormones or with the same mediators involved in major depression[8].

Increased markers of inflammation were found in women with lifetime exposure to trauma representing a so-called biological scare of previous trauma[9]. Moreover, mothers who were victim of childhood trauma were consistently found at risk of PND[10]. Accordingly, the NICE guidelines of antenatal and postnatal mental health strongly recommended the assessment of previous experience of trauma or childhood maltreatment in the perinatal period[11].

FINDINGS FROM PREVIOUS STUDIES

In animal models, the administration of inflammatory cytokines reduced the synthesis of the brain-derived neurotrophic factor (BDNF)[12], which regulates the survival of neurons, modulates synaptic plasticity[13], and increases the susceptibility to depressive disorders[14]. Altered BDNF expression is conceived as a "state" marker of depression, improving with symptoms remission and antidepressant treatment[15]. Brain and peripheral elevated pro-inflammatory biomarkers as IL-6, IL-1 , and TNF-α, and acute-phase proteins, such as C-reactive protein (CRP), were associated with perinatal depression onset, symptoms, and depression-related cognitive deficits. Nonetheless, the results varied widely with data collected at different time points across the perinatal period, since the immune system activation markedly changes during pregnancy and lactation. It was documented that, in normal pregnancy, the first and third trimesters were proinflammatory phases associated with a rise in the secretion of glucocorticoids; by contrast, the second trimester required an inflammatory state leading to fetal growth and development[19]. A prospective longitudinal cohort study in low-income pregnant women did not report a significant association between depression and TNF-α and IL-6 levels at both early and late gestation[20]. On the other hand, data from the Finn Brain Birth cohort study suggested that IL-6 and TNF-α serum concentrations were unrelated to depressive symptoms at the second trimester of pregnancy[21]. In a longitudinal study of women at high risk for developing postpartum depression, CRP and IL-6 were measured. Serum CRP levels were correlated with different phenotypes of depression at the third trimester of pregnancy and at the post-partum period, respectively[22]. In a more recent study investigating inflammation and PND, cytokines levels were increased at the third trimester of pregnancy in women with comorbid depressive and anxious symptoms, and differences emerged based on ethnicity and body weight[23].

Taken together these findings highlighted that it is still necessary to clarify the relationship between inflammation and PND in terms of timing of depression onset and severity of symptoms. Moreover, the pro-inflammatory changes were found in individuals with a history of childhood trauma irrespective of major depression diagnosis[24]. Trauma may facilitate the development of PND in two ways: increasing vulnerability, via the psychosocial[25,26] and immune activation of the hypothalamic-pituitary-adrenal axis (HPA)[27] that constitutes the biological scar of trauma exposure; and affecting the protective factor against the development of psychopathology, such as resilience[28]. To date, literature exploring the association between neuroinflammation, PND, and trauma yielded conflicting findings. It was documented that early traumatic exposure may result in persistently elevated TNF-α levels throughout pregnancy, despite the inflammatory pattern not being associated with the risk of depression[20]. While another study reported that childhood physical abuse and emotional neglect were linked to increased CRP in pregnancy, no correlation was found between TNF-α and antenatal depression[29].

In this study, we explored the inflammatory patterns associated with the underlying neurobiology of PND, measuring inflammation activity markers such as cytokines (IL-6, TNF-α, IFN-γ), acute phase proteins (CRP) and erythrocyte sedimentation rate (ESR), HPA axis activity index (cortisol) and neurotrophic factors (BDNF) in women at the second trimester of pregnancy (at 22 to 24 weeks gestational age). Moreover, we tested whether the biological markers were correlated with the severity of PND, trauma history, and resilience level.

MATERIAL AND METHODS

The data in this study comes from a collaboration between the University of Rome "Tor Vergata" and Sapienza - University of Rome, which was promoted by the non-profit Volunteers Association of Tor Vergata Hospital organization with the aim of increasing screening, detection, and treatment of perinatal depression. We recruited two healthy volunteers control groups. The absence of either psychopathology or personal/familiar history of trauma was confirmed using clinical interview according to DSM-5 criteria. Since the inflammatory measures can be influenced by the pregnancy status, the two healthy groups included women during pregnancy and outside the perinatal phase. A final

sample of four groups of women (n=79) including two groups of patients and two control groups without a personal and familial history of psychiatric disorders and lifetime trauma exposure were enrolled: i) 20 women at the second trimester of pregnancy (at 22 to 24 weeks gestational age) with PND diagnosis and trauma exposure (TRAUMA), ii) 19 women at the second trimester of pregnancy (at 22 to 24 weeks gestational age) with PND and without trauma history (no-TRAUMA), iii) 20 healthy volunteers (HV) at the second trimester of pregnancy (at 22 to 24 weeks gestational age) and iv) 20 healthy volunteers outside the perinatal period (HV).

Women with autoimmune diseases, obstetric illnesses, or a twin pregnancy were excluded from the study. The study was performed in accordance with the Helsinki declaration standards and was approved by the Ethical Review Board of the University of Rome "Tor Vergata" and by the Ethical Review Board of the affiliated Sapienza - University of Rome. All participants were able to understand the aims and procedures of the study and signed informed consent.

Clinical interview and psychometric instruments

The presence or absence of psychopathology was assessed by a clinical interview according to the DSM-5 criteria. Accordingly, the diagnosis of PND was made using clinical interview while the severity of current depressive symptoms was assessed with the psychometric instrument. The trauma history was also investigated with clinical interview, and it was confirmed using the self-report questionnaire.

The sociodemographic data sheet included age, education, marital status, nationality, employment, personal and family history of psychiatric disorders, previous and current medical conditions, and gynecological information (previous pregnancies, abortions, assisted pregnancy, gestational week, complications of current pregnancy).

The Italian version of the Edinburgh Postnatal Depression Scale (EPDS) was administered as a screening tool for current symptoms of PND[30,31]. It consists of 10 items and four possible answers (with a score per single item ranging from 0 to 3). In this study, a score of 12 or higher was used as the cut-off for clinically relevant PND[32]).

Exposure to traumatic events was assessed using the Italian version of the Inventory of Traumatic experiences (TEC)[33,34]. It is a self-report scale that investigates 29 different types of potentially traumatic events. Scores can be calculated cumulatively or by clusters of traumas: emotional neglect, emotional abuse, physical abuse, and sexual abuse.

Resilience was assessed using the Italian version of the Connor-Davidson Resilience Scale (CD-RISC), a 25-item, 5-point Likert scale assessment of "personal qualities that enable one to thrive in the face of adversity". Scores range from 0 (not true at all) to 4 (true nearly all the time) with a higher score (total score ranges from 0 to 100) indicating higher resilience[35,36].

Blood sampling

Blood sampling took place in the morning between approximately 8:00 and 10:00 a.m. Participants were asked to avoid food intake for at least 2 h beforehand. As far as possible, the sampling time was kept constant for each subject. Blood samples were briefly swayed and kept at room temperature for 30 min to be, then, centrifuged before serum was pipetted, aliquoted, and stored at -80 °C.

The acute phase reactants CRP and ESR and serum cortisol were assessed using standard procedure. For the quantification of TNF-α levels in serum, the TNF-α ELISA DRG Diagnostics kit was used, following the manufacturer's instructions.

For quantifying serum IL-6 levels the DRG Diagnostics IL-6 ELISA kit was used, according to the manufacturer's instructions.

For the quantification of BDNF levels in serum, the Quantikine ELISA – Human Free BDNF (R&D Systems) kit was used, following the manufacturer's instructions.

To minimize assay variance, the protein concentrations of all subjects were measured on the same day. All experiments were performed in duplicate.

Statistical analysis

A priori power analysis was used to calculate the sample size that may detect the possible effect of cytokines in the four groups with a given α and power (1-β). Considered a given α=0.05 (two-tailed) and (1-β) =0.95, a sample size of 76 individuals was computed. Shapiro-Wilk test was used to test the assumption of normal distribution and the Levene test was used to evaluate homogeneity of variances among the groups. All the continuous variables were normally distributed. Descriptive statistics were used to illustrate the characteristics of the study samples. Variables were treated either as continuous (age, educational status, biological marker levels, TEC, EPDS, and CD-RISC scores) or binary (couple relationship, employment, smoking, psychotherapy, antidepressant use, medical comorbidity, primigravida). Chi-Square test was used to test relationships between categorical variables. The Student's t-test was used to compare the differences between the mean values of continuous variables. The one-way ANOVA analysis was performed to detect significant differences between the demographic and psychometric measures and groups and the Bonferroni-corrected post-hoc tests were performed to compare the cytokine and trauma values and groups. The logistic regression analyses were performed to evaluate the relationship between biological markers (independent variables), and the EPDS≥12 or EPDS<12 (dependent variable) and obtaining crude odds ratios (ORs). This statistical method was chosen to analyze the effects of independent variables on a binary dependent variable in terms of the probability of being in one of the two categories as opposed to the other. We used the boxplot with the aim of depicting graphically groups of numerical data using their quartiles. A boxplot is a standardized way of displaying the dataset based on a five-number summary: the minimum, the maximum, the sample median, and the first and third quartiles. The variables that were correlated at the significance level of $p<.05$ were included in the logistic regression analysis (37,38). Statistical analyses were performed using GraphPad Prism 8 (GraphPad Software's Inc. USA) and IBM SPSS software Statistics version 26. The sample size calculation was performed using G*Power. For all the statistical analyses, the p-value <0.05 was considered significant.

RESULTS

We conducted the a priori power analysis, considering a given α=0.05 (two-tailed) and (1-β) =0.95 and effect size

Table 1. Demographic and psychometrics of the Sample - [mean (standard deviation)] - (n=79).

		No trauma (n=19)		Trauma (n=20)		HV in pregnancy (n=20)				HV no pregnancy (n=20)			
Variable	**Value**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**Missed (No.)**	**% missed**	**No.**	**%**	**Missed (No.)**	**% missed**	**p-value**
Age, years; mean (SD)		30.7 (5.1)		35.7 (5.0)		30.4 (4.3)				29.6 (4.8)				<0.001
Education, years; mean (SD)		13.0 (3.3)		14.5 (2.9)		14.0 (3.9)				16.7 (2.2)				<0.001
Education	Junior high school	4	21.1	1	5.0	3	20	5	25.0	0	0.0	0	0.0	
	High school	11	57.9	12	60.0	6	40			5	25.0			
	Bachelors degree/Post graduate	21.1	7	35.0	6	40			15	75.0				
Couple relationship	Single/separated/divorced	10.5	1	5.0	11	73.3	5	25.0	13	65.0	0	0.0		
	Married/cohabiting	17	89.5	19	95.0	4	26.7			7	35.0			
Occupation	Employed full/part time	17	89.5	15	75.0	5	31.3	4	20.0	10	50.0			
	Unemployed	2	10.5	5	25.0	11	68.8			10	50.0			
Smoking	Yes	4	21.1	4	20.0	0	0.0	12	60.0					
	No	15	78.9	16	80.0	8	100.0							
Psycotherapy	Yes	9	47.4	11	55.0									
	No	10	52.6	9	45.0									
Antidepressants	Yes	13	68.4	16	80.0	0	0.0	19	95.0					
	No	6	31.6	4	20.0	1	100.0							
Medical comorbidity	Yes	1	5.3	5	25.0	2	28.6	13	65.0					
	No	18	94.7	15	75.0	5	71.4							
Primigravida	Yes	16	84.2	13	65.0	4	50.0	12	60.0					
	No	3	15.8	7	35.0	4	50.0							
CD-RISC; mean (SD)	Yes	42.4	(18.7)	33.4	(15.4)		71.3	(8.6)		68.4	(8.3)			<0.001

HV: healthy volunteers; SD: standard deviation; CD-RISC: Connor-Davidson Resilience Scale; p-value: one way ANOVA; p<0.05 significant

F=0.50. The sample size of 76 participants was computed. The EPDS, TEC and CD-RISC measures showed internal consistency (Chronbach's alpha: 0.71, 0.77, 0.75 respectively). Demographic and psychometric characteristics of the four groups of participants (i.e. women with PND without trauma (no TRAUMA); women with PND and trauma (TRAUMA); Healthy Volunteers in pregnancy (HV in pregnancy) and healthy volunteers outside perinatal period (HV) were reported in Table 1.

The groups were similar as regards age, educational status, current smoking habits, and medical comorbidities. Marital status and occupation were different among the groups.

The one-way ANOVA analysis showed significant differences between groups in terms of CD-RISC scores (F=34.77; p<0.001), the Bonferroni post-hoc test showed significant pairwise comparisons: NO TRAUMA/HV in pregnancy p<0.001, NO TRAUMA /HV no pregnancy p<0.001, TRAUMA /HV in pregnancy p<0.001, TRAUMA /HV no pregnancy p<0.001). Higher CD-RISC mean score in the HV in pregnancy group was found with respect to the HV no-pregnancy, no TRAUMA, and TRAUMA groups. Women with PND and a history of trauma reported a lower CD-RISC score in comparison to patients without trauma exposure, HV not in pregnancy, and HV in pregnancy, respectively.

Table 2 showed unmatched t-test and Chi-square test results of TEC and EPDS scores between the no TRAUMA and TRAUMA groups. Women with PND and trauma history reported a higher mean TEC total score (p<0.0001), a higher mean emotional neglect-TEC subscale score (p=0.002) and a higher mean EPDS total score (p=0.004) compared to those with no-trauma history (5.7 vs 1.9; 3.6 vs 0.5; 20.1 vs 14.7).

The one-way ANOVA analysis of biological markers in the four groups was reported in table 3. The ERS, CRP and TNF-a results are illustrated in figures 1-3 (Side-by-Side Boxplots). The one-way ANOVA analysis showed a significant difference in the mean values of ERS (F=2.87; p=0.040), the Bonferroni post-hoc test showed significant pairwise comparisons: NO TRAUMA/HV in pregnancy p=0.037, NO TRAUMA/HV no pregnancy p=0.001, TRAUMA/HV no pregnancy p=0.038, CRP (F42=4.05; p=0.010), the Bonferroni post-hoc test showed significant pairwise comparisons:

Table 2. TEC and EPDS differences between the two gropus of patients - [mean (standard deviation)] - (n=39).

		No trauma (n=19)				Trauma (n=20)				
Variable	**Value**	**No.**	**%**	**Missed (No.)**	**% missed**	**No.**	**%**	**Missed (No.)**	**% missed**	**p-value**
TEC total; mean (SD)		1.9 (1.7)		0	0.0	5.7 (2.9)		0	0.0	<0.001
Emotional neglect; mean (SD)		0.5 (1.0)		2	10.5	3.6 (3.6)		2	10.0	0.002
Emotional abuse; mean (SD)		0.5 (1.0)		2	10.5	1.4 (1.8)		2	10.0	0.081
Physical abuse; mean (SD)		0.6 (2.2)		2	10.5	1.5 (2.4)		2	10.0	0.247
EPDS; mean (SD)		14.7 (5.0)		0	0.0	20.1 (5.7)		0	0	0.004
EPDS	EPDS < 12	3	15.8	0	0.0	1	5.0	0	0.0	0.267
	EPDS > 12	16	84.2			19	95.0			

TEC: Traumatic Experiences Checklist; EPDS: Edinburgh Postnatal Depression Scale; SD: standard deviation; p-value: Student t-test, Chi-square; p<0.05 significant

Table 3. Biological markers data (n=79).

	No trauma (n=19)	Trauma (n=20)	HV in pregnancy (n=20)	HV no pregnancy (n=20)	
Variable					**p-value**
ERS mm/h; mean (SD)	36.3 (22.9)	30.9 (14.3)	22.2 (12.0)	17.1 (10.5)	0.040
CRP mg/l; mean (SD)	11.2 (17.3)	2.4 (3.8)	5.5 (9.0)	0.9 (1.6)	0.010
Cortisol ug/dl; mean (SD)	22.2 (8.7)	22.2 (9.3)	23.2 (7.3)	15.9 (7.6)	0.126
IL-6 pg/ml; mean (SD)	7.5 (5.5)	4.3 (3.7)	10.8 (11.9)	5.8 (10.8)	0.128
TNF-α pg/ml; mean (SD)	4.5 (1.4)	5.0 (2.6)	3.4 (2.1)	2.5 (1.6)	0.001
BDNF ng/ml; mean (SD)	19.5 (3.5)	21.7 (4.7)	22.2 (3.9)	23.6 (6.5)	0.226

SD: standard deviation; p-value: One way ANOVA; p<0.05 significant

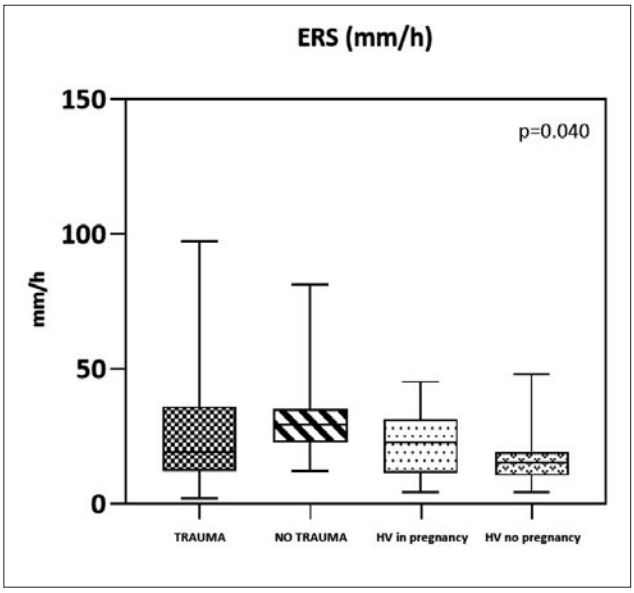

Figure 1

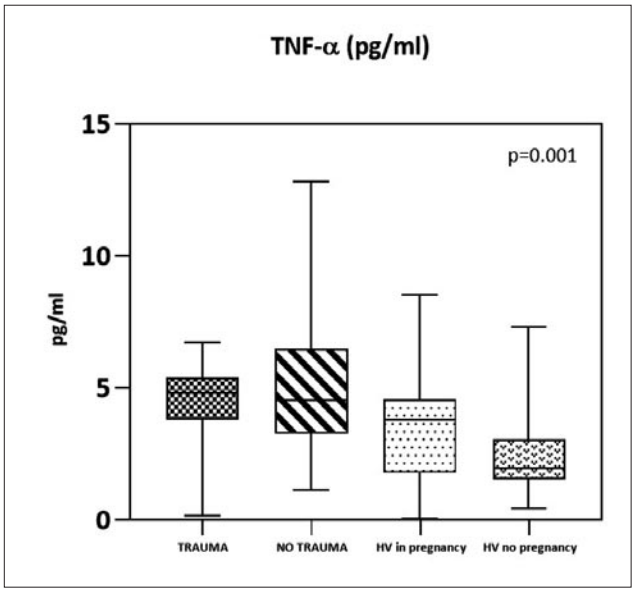

Figure 3

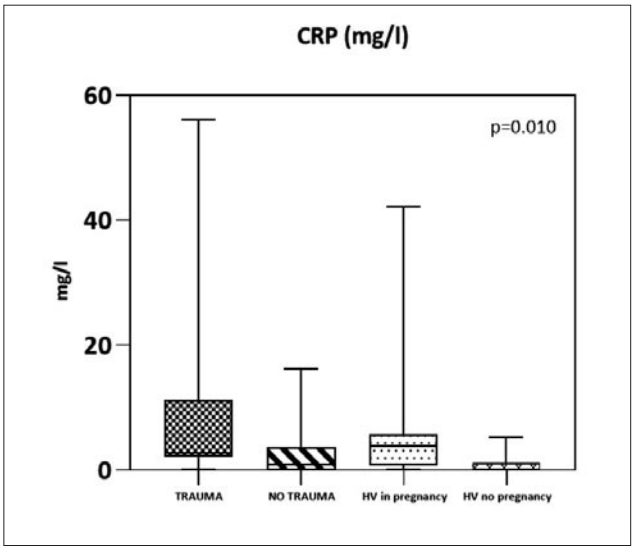

Figure 2

Figures 1-3. Side-by-Side Boxplots representing the one-way ANOVA analysis of biological markers (ERS, CRP, Cortisol, IL-6, TNF-α, BDNF) in the four groups of women (Trauma, No trauma, HV in pregnancy and HV no pregnancy).

NO TRAUMA/HV no pregnancy p = 0.011) and TNF-α (F=6.07; p=0.001), the Bonferroni post-hoc test showed significant pairwise comparisons: NO TRAUMA/HV no pregnancy p=0.019, TRAUMA/HV no pregnancy p=0.001). Women with PND and no trauma history reported higher ERS mean levels compared to those in the TRAUMA section, HV in pregnancy, and HV no-pregnancy groups, respectively. The CRP mean level was higher in the no TRAUMA group compared to the HV in pregnancy, TRAUMA, and HV no-pregnancy groups, respectively. The TNF-α mean level was higher in the TRAUMA group compared to the no TRAUMA, the HV in pregnancy, and the HV no-pregnancy groups, respectively. The mean differences of cortisol, IL-6, and BDNF were not statistically significant.

The adjusted logistic regression analysis was represented in table 4. In the model, the EPDS total score of the two groups of women with PND (with and without trauma) was the dependent variable and the biological markers (VES, PCR, cortisol, IL-6, TNF-α, and BDNF) were the independent variables. The results were not significant. The TNF-α OR was 1.856 (p=0.053)

Table 4. Logistic regression (EPDS is the dependent variable)

	EPDS	
Variable	**OR (95% CI)**	**p-value**
ERS	1.064 (0.982-1.153)	0.130
CRP	0.972 (0.864-1.094)	0.643
Cortisol	0.936 (0.824-1.062)	0.303
IL-6	0.987 (0.854-1.140)	0.857
TNF-α	1.856 (0.993-3.470)	0.053
BDNF	1.003 (0.822-1.225)	0.974
p<0.05 significant		

DISCUSSION

Summary of the study findings

Our main result was that pregnant women with lifetime trauma were characterized by increased depressive symptoms and decreased resilience level compared to women without trauma exposure. Moreover, in a recent study, we found that adverse life-events were related to the onset of depression during pregnancy compared to the postnatal period[6]. In this study, we documented a lower resilience level in women with PND and trauma exposure compared to those with depression alone or to the control group. In contrast with literature data, inflammatory markers were not associated with the severity of depressive symptoms[39]. On the other hand, comparing our four groups of participants, we documented a significant increase in the acute phase markers, ESR and CRP, in pregnant women suffering from PND and without a history of trauma and the high level of TNF-α in patients with either depression or trauma. In this way, the basal levels of systemic inflammatory activity were increased in pregnant women with depression, as it was proven by ESR, CRP, but the pro-inflammatory cytokine TNF-α levels were higher in women with PND and history of trauma.

Theoretical considerations

Accordingly to literature data, it was reported that women who experienced trauma, especially childhood sexual abuse, physical injury, unexpected loss or illness of someone with whom they had a close relationship were more vulnerable to PND, with an exaggerated effect when the trauma was varied[40-42]. The detrimental effect of trauma may also impair the fetal development and the mother-baby bond with offspring long-term sequelae[43,44]. It was argued that lifetime exposure to trauma were strongly associated to poor maternal perinatal health and dysregulation in several biological systems[45]. Maternal trauma affects the quality of the fetal environment during sensitive periods of neural development ruling the vulnerability of offspring to a broad range of diseases[46]. Following our data, we believe that trauma would benefit of great attention from clinicians because it may affect the onset (i.e. during pregnancy) and the severity of PND. In fact, in our sample women with trauma history were affected by depression starting from pregnancy and reported more severe symptoms compared to the non-trauma group. Accordingly, the last updates of the perinatal mental health NICE guideline is, strongly, recommended to assess current and lifetime trauma exposure due to their strong association with depression development, the potential threat to a healthy pregnancy, and the availability of effective treatments[47].

The perinatal period is a time of unique challenge for women who are asked to improve the ability to respond to unpredictable environmental stress and to adapt to the new role of motherhood[48]. In this view, resilience is of critical importance to the new mothers by helping them to overcome the possible challenges of the perinatal phase and to cope with the negative effects of previous trauma. Although is well-known that trauma may affect individual resilience[49], our finding among pregnant women is compelling either because resilience may strengthen women or because resilience may mitigate the well-documented effect of childhood trauma on maternal illness[46] and the intergenerational transmission of trauma from mother to child[47]. Thus, particularly in light of our results, resilience-enhancing interventions may be extremely helpful for depressed mothers[50] representing a new focus of treatment that needs to be fostered.

With regards to the inflammatory patterns associated with PND, we obtained conflicting results. The immune response that is expressed by the acute phase proteins and TNF-α was increased in the two groups of patients with PND compared to healthy pregnant and non-pregnant control groups. Even though, contrary to our expectations, only the TNF-α values were higher women with history of trauma. As far as concerns the remaining, non-significant, biological markers, we found no differences concerning cortisol, BDNF and IL-6 levels among the study samples. Despite this, researchers previously recognized that mid-pregnancy depression was strongly associated with increased cortisol[51]. Alteration of the HPA axis was also conceived as a robust marker of the negative effect of antenatal maternal emotional status on fetal neurodevelopment since cortisol can pass through the placenta[52]. Moreover, low BDNF level was associated with late pregnancy depression, multiple stressful life events, and suicide risk[53]. Possible answers to the unexpected results of this study may rely on the high prevalence of antidepressant treatment in our sample (72.5% of patients) which may have affected the HPA axis activity and neurogenesis through various molecular mechanisms[54]. For the same reasons, we could not demonstrate the role of IL-6, contrary to the studies highlighting that IL-6 was a useful biomarker of risk in perinatal depression[55,56].

Moreover, keeping with the theory of subgroups of PND[57], not all phenotypes of depression are associated with elevated inflammation levels[58]. It was previously noted that varied assessment measures of depression severity and clusters of symptoms were correlated with distinct immune markers[59]. Accordingly, it is possible that a subgroup of women with "inflamed depression" was included in our sample, but we could not perform a further stratification of groups, due to the small number of participants.

We must admit the limitations of this study. Notably, the between-group differences in biomarkers could, apparently, be overcome by other factors influencing inflammation, principally the body mass index, Mediterranean diet pattern and

adherence to pharmacological treatments[29,60,61]. However, we excluded women with inflammatory disorders or obstetric complications as potential confounding factors.

Nevertheless, comparing healthy women' measures, our findings of the increase of ESR and CRP in women with PND and the higher TNF-α level in those with trauma exposure supported the inflammatory theory of PND. The significant biological markers of our study may either be involved in the development of the "sickness behaviors", namely perinatal depressive symptoms or express the biological response to previous trauma[8,62].

Given the assumption that women perinatal disorders influence mental health risks for the mother and offspring, the search to find reliable biomarkers in affected mothers is a test for medical researchers to develop preventive strategies and appropriate treatments.

CONCLUSIONS

We found that a history of trauma is associated with a more severe clinical phenotype of PND while it differentiates pregnant women suffering from depression affecting biological markers that may drive depression pathogenesis, remission, and treatment response. Pertinent screening and therapeutic approaches should be encouraged.

Availability of data and material: the dataset is a property of the nonprofit Volunteers Association of "Tor Vergata" Hospital in Rome, Italy and it is available from the corresponding author on reasonable request.

Ethics approval and consent to participate: all the participants provided written informed consent. The study was performed in accordance with the Helsinki declaration standards and was approved by the Institutional Ethics Review Committee of the University of Rome "Tor Vergata".

Consent for publication: all authors gave consent to publication.

Competing interests: the authors declared no competing interests.

Authors' contributions: Y.B., A.D.S. and C.N. designed the study. Y.B., F.A., N.G. and V.L.S. collected the data and completed the database. E.B. wrote the manuscript and supervised the database. All authors revised and approved the final version of the manuscript.

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