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Decreased plasma concentrations of brain-derived neurotrophic factor in preeclampsia

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ABSTRACT

Background: Preeclampsia (PE) is a disease characterized by excessive maternal inflammatory response. Early studies suggested that brain-derived neurotrophic factor (BDNF) modulates inflammation. The main objective of this study was to investigate BDNF plasma concentrations in PE women and to compare with BDNF concentrations from normotensive pregnant women. We also investigated the association among the plasma concentrations of BDNF and inflammatory mediators, and maternal clinical features.
Methods: BDNF plasma concentrations were measured by ELISA in 38 PE women (17 early onset and 21 late onset) and in 20 normotensive pregnant women (Norm) matched for gestational age (Norm < 34 weeks: $n = 8$; Norm ≥ 34 weeks: $n = 12$). Correlation analyses between laboratory parameters and clinical characteristics were evaluated through Spearman's coefficients.
Results: BDNF concentration was lower in PE women than in normotensive pregnant women, but no difference was detected between the subgroups of PE women and normotensive pregnant women. BDNF correlated negatively with annexin A1, and positively with body mass index and diastolic blood pressure. No correlation was significant in normotensive pregnant women.
Conclusions: Lower BDNF plasma concentrations and cross-talk between BDNF and AnxA1 signaling pathways might be involved in PE pathogenesis.

1. Introduction

Preeclampsia (PE) is a hypertensive and multi-system disease of pregnancy that represents one of the leading causes of maternal and fetal morbidity/mortality worldwide [1]. Although its pathophysiology is not fully elucidated, a series of evidence suggests that defective placentation is the initiating event which contributes to systemic endothelial dysfunction, oxidative stress and inflammation [2]. PE can be classified according to the gestational age (GA) of clinical symptoms development in early onset (GA < 34 weeks) and late onset (GA ≥ 34 weeks) [3].

Brain-derived neurotrophic factor (BDNF) is a growth factor that belongs to the neurotrophin family, and is abundantly expressed in the central and peripheral nervous systems. BDNF signals through tyrosine kinase B (TrkB) receptor to regulate neuronal development, function and plasticity [4]. BDNF is also expressed in non-neuronal tissues [5]. In addition to neuroprotective effects, BDNF stimulates angiogenesis, placental development and fetal growth [6,7]. It has also been shown that BDNF expression is modulated by oxidative stress and inflammation [8,9]. Conversely, BDNF is able to modulate inflammatory responses [10–12]. Therefore, altered concentrations of BDNF could contribute to PE pathogenesis.

Previous studies that evaluated BDNF circulating concentrations in PE women have reported either lower, higher or similar concentrations when compared with normotensive pregnant women [13–16]. We aimed to investigate BDNF plasma concentrations in women with early onset PE and late onset PE and in normotensive pregnant women matched for gestational age and socioeconomic background. We also analyzed the relationship among the concentration of BDNF, inflammatory molecules (soluble tumor necrosis factor receptor-1 - sTNF-R1 and annexin A1 - AnxA1) evaluated in previous studies [17,18] and maternal clinical features in order to better understand the role of BDNF in PE pathogenesis.

Abbreviations: AnxA1, annexin A1; BDNF, brain-derived neurotrophic factor; DBP, diastolic blood pressure; GA, gestational age; GWG, gestational weight gain; Norm, normotensive pregnant women; PE, preeclampsia/preeclamptic; SBP, systolic blood pressure; sTNF-R1, soluble tumor necrosis factor receptor-1; TNF-α, tumor necrosis factor alpha; TrkB, tyrosine kinase B.

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2. Materials and methods

2.1. Ethics

The procedures in this study were in accordance with Ethics Committees of Universidade Federal de Minas Gerais and the participating hospitals (Santa Casa de Misericórdia de Belo Horizonte: Fundação Hospitalar do Estado de Minas Gerais; Hospital Municipal Odilon Behrens), and a written informed consent was obtained from each participant.

2.2. Patients

This study included 38 PE women and 20 normotensive pregnant women in the third trimester of pregnancy who were recruited from Brazilian public hospitals. PE women were stratified in early onset PE ($n = 17$) and in late onset PE ($n = 21$) subgroups [3]. Normotensive pregnant women were stratified in 2 subgroups considering the cut-off of 34 weeks (Norm < 34 weeks: $n = 8$; Norm ≥ 34 weeks: $n = 12$) to match the subgroups of PE women.

PE was defined by systolic and diastolic blood pressure ≥ 140/90-mm Hg after 20 weeks of gestation in a previously normotensive women, confirmed by 2 consecutive readings at least 4 h apart in association with proteinuria (≥300 mg/24 h or ≥1 + reading on dipstick in a random urine specimen) and/or evidence of end-organ dysfunction (thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, cerebral or visual disturbances) [1]. Normotensive pregnant women had blood pressure < 120/80 mm Hg and no history of hypertension. All women were matched according to socioeconomic status. The exclusion criteria for both groups were: chronic hypertension, obesity (grades II and III) [19], diabetes, cancer, homeostatic abnormalities, infectious, cardiovascular, autoimmune, renal, hepatic, psychiatric and neurological diseases.

2.3. Sample collection, processing and storing

Five milliliters of maternal venous blood were collected in EDTA anticoagulant-coated tubes (BD Vacutainer). The blood was centrifuged at 3000*g* for 15 min at room temperature to separate the plasma. The plasma aliquots were stored at −80 °C until analyses.

2.4. BDNF measurement

BDNF plasma concentrations were measured by ELISA using a commercial available kit (R&D Systems) according to the manufacturer's instructions and were reported as pg/ml. The BDNF antibody used in this assay detects human BDNF in ELISA, and no cross-reactivity or interference was observed with recombinant human glial cell-derived neurotrophic factor, β-nerve growth factor, neurotrofin 3 or neurotrofin 4.

2.5. Statistical analysis

The data were analyzed using SPSS software ver 19.0. The normality of continuous variables was assessed using Shapiro-Wilk's W-test. Continuous variables not normally distributed were analyzed by Kruskal-Wallis test. When differences were detected among the groups, they were compared 2 × 2 with the Mann-Whitney *U* test or Mann-Whitney *U* test followed by Bonferroni's correction (4 groups). The comparison of continuous variables with normal distribution was performed by analysis of variance (ANOVA) test with *post hoc* LSD test (4 groups) or Student's *t*-test (2 groups). The comparison of categorical variables was performed by Pearson χ^2 test. Parametric data were expressed as mean ± SD, non-parametric data as median (25th–75th percentiles) and categorical variables as absolute number (percentage). Spearman's correlation coefficients (r_s) were used to investigate the possible correlations among the plasma concentrations of BDNF and inflammatory mediators evaluated in previous studies [17,18], and clinical parameters in PE women and in normotensive pregnant women. A *P*-value <0.05 denoted statistical significance.

3. Results

3.1. Clinical characteristics

Table 1 shows the clinical characteristics of the studied groups. No significant difference was detected in age, body mass index (BMI) before pregnancy, gestational weight gain (GWG) and GA at blood collection between normotensive pregnant women and PE women. PE group had lower number of gestations ($P = 0.009$) and higher number of primiparas ($P = 0.013$) than normotensive group. As expected, systolic and diastolic blood pressures (SBP and DBP, respectively) were significantly increased in PE women (all $P < 0.001$). There was no significant difference in educational degree between the groups.

The clinical characteristics of the subgroups of normotensive pregnant women and PE women are displayed in Table 2. No differences were found for age, BMI before pregnancy, number of gestations, number of primiparas and educational degree among the subgroups. Pregnant women with late onset PE had higher GWG than normotensive pregnant women with GA < 34 weeks ($P = 0.004$). As expected, GA at blood collection was higher in late onset PE when compared with early onset PE and normotensive pregnant women with GA < 34 weeks, and in normotensive pregnant women with GA ≥ 34 weeks when compared with early onset PE and normotensive pregnant women with GA < 34 weeks (all $P < 0.001$). In addition, SBP and DBP were higher in early onset PE and late onset PE when compared with normotensive pregnant women with GA < 34 weeks and normotensive pregnant women with GA ≥ 34 weeks (all $P < 0.001$). No participant in this study was illiterate or had completed higher education.

3.2. BDNF plasma concentrations

BDNF plasma concentrations were lower in PE women [2970 (2021–5403) pg/ml] than in normotensive pregnant women [4913 (2548–9551) pg/ml] ($P = 0.029$) (Fig. 1). No significant difference was

Table 1
Clinical characteristics of normotensive pregnant women and PE women.

Variables	Norm ($n = 20$)	PE ($n = 38$)	*P*
Age (y)[a]	23 (19–27)	26 (21–29)	0.325
BMI (kg/m^2)[b]	22.4 ± 3.5	23.5 ± 2.9	0.872
GWG (kg)[a]	10.4 (8.5–12.7)	12.5 (9.3–18.7)	0.062
GA (weeks)[a]	35 (30–39)	34 (32–38)	0.658
Parity			
Gravidity (n)[a]	2 (1–3)	1 (1–2)	0.009
Primiparas (%)[c]	5 (25)	23 (61)	0.013*
SBP (mm Hg)[a]	110 (100−110)	160 (150–170)	<0.001***
DBP (mm Hg)[a]	70 (70–70)	102 (100−111)	<0.001***
Education[c]			0.094++
Informed (%)	20 (100)	28 (74)	
Elementary school (%)+	1 (5)	4 (14)	
Middle school (%)+	11 (55)	7 (25)	
High school (%)+	8 (40)	17 (61)	
Not informed (%)	0 (0)	10 (26)	

Abbreviations: BMO before pregnancy; GWG, gestational weight gain; GA, gestational age at blood collection; n, number/sample size; SBP, systolic blood pressure; DBP, diastolic blood pressure; Norm, normotensive pregnant women; PE, preeclamptic women.
[a] Mann-Whitney *U* test; data are presented as median (25th–75th percentiles).
[b] Student's *t*-test; data are presented as mean ± SD.
[c] Pearson χ^2 test; data are presented as number (percentage).
* $P < 0.05$.
*** $P < 0.001$.
+ The percentage of each educational variable was calculated considering the total of patients who informed their educational degree in each group.
++ The analysis of education considered only patients who informed their educational degree.

Table 2
Clinical characteristics of the subgroups of normotensive pregnant women and PE women.

Variables	Norm < 34 wks ($n = 8$)	Norm ≥ 34 wks ($n = 12$)	Early onset PE ($n = 17$)	Late onset PE ($n = 21$)
Age (y)[1]	22 (19–26)	24 (19–30)	24 (20 − 30)	26 (21–29)
BMI (kg/m^2)[2]	21.1 ± 2.4	23.4 ± 3.9	23.6 ± 2.7	23.4 ± 3.1
GWG (kg)[1]	9.4 (6.4–11.0)[a]	12.3 (9.0–15.7)	12.0 (7.5–16.2)	14.0 (10.3–22.8)
GA (weeks)[1]	30 (29–31)[a,b]	39 (36–40)[c]	31 (30 − 33)	37 (34–39)
Parity				
Gravidity (n)[1]	2 (1–3)	2 (2–3)	1 (1–2)	1 (1–2)
Primiparas (%)[3]	3 (38)	2 (17)	10 (59)	13 (62)
SBP (mm Hg)[1]	110 (100–110)[a,d]	110 (100–110)[c,e]	170 (160–180)	155 (140–170)
DBP (mm Hg)[1]	70 (70–70)[a,d]	70 (70–70)[c,e]	110 (100 − 120)	100 (100–110)
Education[3]				
Informed (%)	8 (100)	12 (100)	13 (76)	15 (71)
Elementary school (%)[+]	0 (0)	1(8)	1 (8)	3 (20)
Middle school (%)[+]	5 (63)	6 (50)	5 (38)	2 (13)
High school (%)[+]	3 (37)	5 (42)	7 (54)	10 (67)
Not informed (%)	0 (0)	0 (0)	4 (24)	6 (29)

Abbreviations: GWG, gestational weight gain; GA, gestational age at blood collection; n, number/sample size; SBP, systolic blood pressure; DBP, diastolic blood pressure; Norm, normotensive pregnant women; wks, weeks; PE, preeclamptic women.
[1] Kruskal-Wallis/Mann-Whitney *U* test with Bonferroni's correction; data are presented as median (25th–75th percentiles).
[2] ANOVA test with *post hoc* LSD test; data are presented as mean ± standard deviation.
[3] Pearson χ^2 test. Data are presented as number (percentage).
[a] $P < 0.0125$ (norm < 34 wks *vs.* late onset PE).
[b] $P < 0.0125$ (norm < 34 wks *vs.* norm ≥ 34 wks).
[c] $P < 0.0125$ (norm ≥ 34 wks *vs.* early onset PE).
[d] $P < 0.0125$ (norm < 34 wks *vs.* early onset PE).
[e] $P < 0.0125$ (norm ≥ 34 wks *vs.* late onset PE).
[+] The percentage of each educational variable was calculated considering the total of patients who informed their educational degree in each subgroup. The analysis of education considered only patients who informed their educational degree.

detected between the subgroups of early onset PE [3651 (2327–6575) pg/ml] *vs.* late onset PE [2548 (1748–5024) pg/ml], early onset PE *vs.* norm < 34 weeks [6803 (3543–9551) pg/ml], late onset PE *vs.* norm ≥ 34 weeks [4212 (2240–10,090) pg/ml] and norm < 34 weeks *vs.* norm ≥ 34 weeks.

3.3. Correlations among BDNF, sTNF-R1, AnxA1 and clinical characteristics

In previous studies from our group, PE women had higher plasma concentrations of sTNF-R1 and AnxA1 than normotensive pregnant women [17,18]. Considering the possible role of BDNF in modulating inflammatory responses [10–12], we evaluated the potential association between the plasma concentrations of BDNF and these 2 inflammatory molecules in PE women and in normotensive pregnant women. BDNF showed a negative correlation with AnxA1, but no significant correlation was detected between BDNF and sTNF-R1 in PE women. BDNF also correlated positively with BMI and DBP in these women. There were no further statistical correlations among BDNF and other clinical parameters in PE women. No correlation was significant in normotensive pregnant women. The significant correlations are shown in Fig. 2.

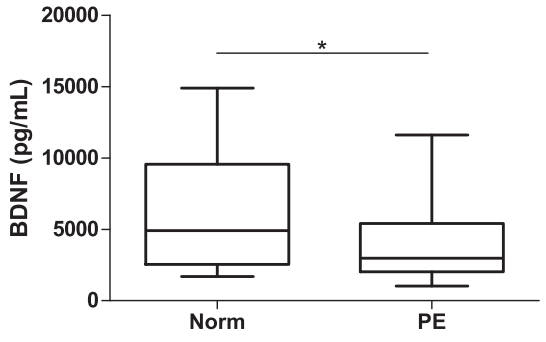

Fig. 1. BDNF plasma concentrations in normotensive pregnant women and in PE women. Lines within the boxes represent the median values for BDNF; top and bottom lines of the boxes represent 25th and 75th percentiles, and upper and lower bars outside the boxes represent maximum and minimum values, respectively. BDNF concentrations are expressed as pg/ml (picograms/ml). Plasma concentrations of BDNF were lower in PE women than in normotensive pregnant women. Abbreviations: BDNF, brain-derived neurotrophic factor; Norm, normotensive pregnant women; PE, preeclamptic women. *$P < 0.05$ (Mann-Whitney *U* test).

4. Discussion

We found lower plasma concentrations of BDNF in PE women when compared with normotensive pregnant women. These findings are in agreement with 2 previous studies [13,14], although higher or similar plasma concentrations of BDNF have also been reported [15,16]. It is noteworthy that BDNF circulating concentrations can be influenced by health-related lifestyle, like cigarettes and alcohol use [20–22]. The divergent results in the literature might also have been biased by differences in dietary habits of the studied populations, which are also known to influence BDNF concentrations.

Down-regulation of placental BDNF gene expression has been reported in PE women [14]. Decreased BDNF concentrations in PE women might be a consequence of defective immune and oxidant/antioxidant mechanisms along with decreased concentrations of endogenous omega-3 fatty acids [8,9,23]. Deficient BDNF concentrations might interfere with angiogenesis, placental development and fetal growth, therefore this neurotrophin has the potential to be involved in PE pathogenesis [6,7]. Moreover, Postma et al. suggested that persistent low BDNF circulating concentrations after pregnancy in women who had PE might be associated with maternal cognitive impairment later in life [24].

PE is a complex disease with variable clinical presentations and pathological features. The disease is classified based on the symptom severity (mild PE and severe PE) and, more recently, on the time of clinical symptoms onset (early onset PE *vs.* late onset PE; preterm PE: <37 weeks *vs.* term PE: ≥37 weeks) [1,3,25]. Much evidence suggests that the sooner the symptoms manifest, usually the worse is the prognosis, corroborating PE classification according to gestational age of clinical symptoms onset [26]. Nevertheless, BDNF plasma concentrations were not significantly different between early and late onset clinical forms in the current study. In addition, D'Souza and coworkers did not report differences in maternal BDNF plasma concentrations between PE women delivering preterm and term PE [13]. Sahay et al.

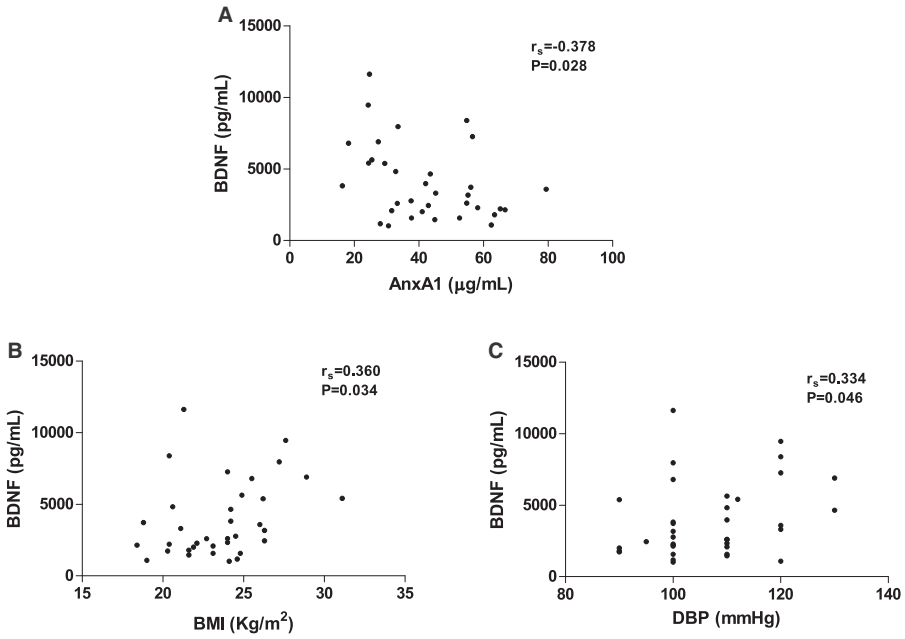

Fig. 2. Significant correlations among BDNF concentrations, AnxA1 concentrations, BMI and DBP in PE women. The closed circles represent the participants in this study. BDNF concentrations correlated negatively with AnxA1 concentrations (A) and positively with BMI before pregnancy (B) and DBP (C) in PE women. Correlation analyses were evaluated by Spearman's correlation coefficients (r_s). Abbreviations BDNF, brain-derived neurotrophic factor; AnxA1, annexin A1; BMI, body mass index; DBP, diastolic blood pressure.

evaluated BDNF protein expression in different regions of human placenta (central maternal, central fetal, peripheral maternal and peripheral fetal) and reported similar BDNF expression between preterm and term PE in each one of these regions. However, BDNF was up-regulated in central maternal region of placenta in preterm PE women when compared with normotensive pregnant women [27]. These data suggest that BDNF circulating concentrations may reflect its placental expression in term PE, but not in preterm PE, and that both placental and circulating BDNF cannot discriminate between early onset PE and late onset PE, as well as preterm PE and term PE.

It has been suggested that BNDF controls inflammation by modulating pro-inflammatory mediators production [28,29]. This is the first study evaluating the association among the plasma concentrations of BDNF, sTNF-R1 and AnxA1 in PE women. In previous studies from our group, PE women had higher plasma concentrations of sTNF-R1 [3479 (3182–4339) *vs.* 3028 (2468–3606) pg/ml, $P = 0.014$] and AnxA1 [43.2 (30.8–57.8) *vs.* 30.1 (19.0–35.7) μg/ml] ($P = 0.026$)] than normotensive pregnant women [17,18].

AnxA1 is a glucocorticoid (GC)-regulated protein endowed with anti-inflammatory actions and that promotes resolution of inflammation [30]. BDNF plasma concentrations correlated negatively with AnxA1 plasma concentrations in PE women in the current study. We hypothesized that AnxA1 plasma concentrations may be increased in PE women who have decreased BDNF plasma concentrations as a compensatory mechanism aiming to temper systemic inflammation. Nineteen (83%) early PE women had a prescription of GC prior to blood collection. We investigated AnxA1 concentrations between early PE women that had [median (25th–75th percentiles): 43.5 (33.0–61.1) μg/ml] or not [49.7 (38.8–56.6) μg/ml] GC prescription, but no significant difference was detected between them. Thus, AnxA1 plasma concentrations were not significantly influenced by GC administration in our study.

It is well established that TNF-R1 has the ability to bind to tumor necrosis factor alpha (TNF-α) and neutralize the effects of this pro-inflammatory cytokine. sTNF-R1 is regarded as an indirect marker of inflammation as it is usually increased in inflammatory conditions characterized by exaggerated TNF-α production, like PE [31,32]. Our group has previously demonstrated that TNF-α and sTNF-R1 plasma concentrations were increased in PE women, which was reinforced by other studies [17,32–34]. Considering that systemic inflammation is exacerbated in PE [2] and that PE women showed decreased BDNF and increased sTNF-R1 plasma concentrations in our studies [17], it was expected a negative correlation between sTNF-R1 and BDNF in the PE women. However, this correlation failed to reach statistical significance. As other pro-inflammatory molecules, like interleukin-1β and lipopolysaccharide, downregulate BDNF expression *in vivo* [35], it can inferred that distinct inflammatory mechanisms may regulate BDNF synthesis and sTNF-R1 concentrations in PE. However, more studies are necessary to clarify how inflammation regulates BDNF concentrations in PE women.

Despite being widely expressed in neurons of the central and peripheral nervous systems, BDNF is also expressed in tissues of gastrointestinal, cardiorespiratory and urogenital systems, especially in epithelial cells [5]. BDNF pattern of expression and ability to modulate synaptic transmission implicate this neurotrophin in regulating cardiovascular responses, such as blood pressure [36]. Indeed, results from *in vivo* experiments indicate that BDNF treatment increases arterial blood pressure by up-regulating angiotensin type-1 receptor and that aortic BDNF up-regulation precedes the development of hypertension in spontaneously hypertensive rats [37,38]. Accordingly, our data showed that among PE women, those with higher BDNF concentrations had higher DBP. By contrast, D'Souza et al. found no association between BDNF concentrations and blood pressure in PE women, while a negative correlation was found between BDNF concentrations and SBP in normotensive pregnant women [14]. These divergences can be explained by differences in blood pressure concentrations between the studied populations. For instance, D'Souza et al. evaluated PE women with lower blood pressure [mean arterial blood pressure at delivery = 110 ± 14 mm Hg] than in our study [121 (117–131) mm Hg]. The normotensive pregnant women in D'Souza et al.'s study also presented higher blood pressure (91 ± 7 mm Hg) comparing to normotensive pregnant women included in our study [83 (80–83) mm Hg].

Our data also showed that BDNF plasma concentrations correlated positively with pre-pregnancy BMI in PE women, but Bienertova-Vasku et al. did not find this correlation [16]. Several lines of evidence suggest that BDNF regulates energy homeostasis by modulating eating behavior and glucose metabolism in peripheral tissues [39]. Lebrun et

al. reported that BDNF treatment reduced food intake and impaired BDNF/TrkB signaling *in vivo* which was associated with hyperphagia and obesity [40]. Roth et al. revealed that BDNF concentrations were higher in patients with obesity than in normal weight subjects and correlated positively with BMI [41]. Altogether these data suggest a compensatory increase in BDNF concentrations in obesity aiming to regulate weight and food intake, probably due to impaired BDNF/TrkB signaling. A positive correlation between BDNF plasma concentrations and BMI has also been reported in patients with bipolar disorder, a disease characterized by low BDNF circulating concentrations [42,43]. Therefore, studies using experimental models of PE will be crucial to clarify the effect of BDNF in metabolic parameters.

Since it was difficult to obtain accurate information about women's smoking and drinking status, we did not evaluate their influence in BDNF plasma concentrations. Furthermore, we did not assess the dietary habits of the studied population, which could also have influenced BDNF plasma concentrations. Besides, BDNF concentrations were measured only in the third trimester of pregnancy, precluding us to conclude whether BDNF altered concentrations might predispose to PE or is a secondary effect of the disease.

5. Conclusions

Our data suggest that BDNF plasma concentrations are lower in PE women as compared to normotensive pregnant women. The significant negative association between BDNF and AnxA1 concentrations highlight the highly complex crosstalk among different signaling pathways in PE pathogenesis.

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