Brain-derived neurotrophic factor (BDNF) in perinatal depression: Side show or pivotal factor?

Saumya Singh [1], Katarine Fereshetyan [2], Susan Shorter [1], Ruslan Paliokha [3], Eliyahu Dremencov [3], Konstantin Yenkoyan [2], Saak V. Ovsepian [1,*]

[1] Faculty of Science and Engineering, University of Greenwich London, Chatham Maritime, Kent ME4 4TB, UK
[2] Neuroscience Laboratory, Cobrain Center, Yerevan State Medical University of M. Heratsi, 0025, Yerevan, Armenia
[3] Centre of Biosciences, Slovak Academy of Sciences, Bratislava, Slovakia

Perinatal depression is the most common psychiatric complication of pregnancy, with its detrimental effects on maternal and infant health widely underrated. There is a pressing need for specific molecular biomarkers, with pregnancy-related decline in brain-derived neurotrophic factor (BDNF) in the blood and downregulation of TrkB receptor in the brain reported in clinical and preclinical studies. In this review, we explore the emerging role of BDNF in reproductive biology and discuss evidence suggesting its deficiency as a risk factor for perinatal depression. With the increasing evidence for restoration of serum BDNF levels by antidepressant therapy, the strengthening association of perinatal depression with deficiency of BDNF supports its potential as a surrogate endpoint for preclinical and clinical studies.

Keywords: TrkB receptor; postpartum depression; fluid biomarker; estradiol; perinatal affective disorder; neuroplasticity; pregnancy

Introduction

Pregnancy invokes considerable adjustments in fundamental physiological processes to ensure fetal development and delivery. These changes are enabled by a complex interplay of neural and hormonal mechanisms, which set off in the first trimester of gestation, evolve during the pregnancy, and revert after parturition. In most cases, functional adjustments associated with pregnancy remain within physiological limits. Occasionally, however, some of the changes exceed the range of normal variations, leading to pathological states [1,2]. Impairments of mental health are among the most common disease conditions related to pregnancy, which are through to be contributed to by alterations in maternal hormones and their effects on brain mechanisms [3]. Short-lived mood disturbances, known as 'baby blues', which occur in 30–75% of postpartum women, are thought to be linked with the dramatic decline in pregnancy hormones, whereas 10–15% of new mothers develop clinical depression [3,4]. In rare cases (1 or 2 in 1000 births), childbirth-related intense neurohumoral stress is followed by postpartum psychosis, a medical emergency warranting critical care [4].

Despite high incidents of perinatal mental disorders, understanding of their mechanisms and treatment options remain limited. Evidence from preclinical and clinical reports suggests that, in addition to changes in gonad hormones, the odds of perinatal mental disorders can be influenced by stress hormones, immune and trophic factors, as well as genetic and environmental effects, which merit systematic studies [3,5,6]. Over the past decade, there has been growing interest in the complex interplay of multiple factors and their interactions, with the view of developing diagnostic and predictive tests. Given its key role in neuronal functions and alterations in several neuropsychiatric disorders, BDNF received much interest as a potential biomarker [7–9].

* *Corresponding author:Ovsepian, S.V. (s.v.ovsepian@gre.ac.uk)*

1359-6446/Crown Copyright © 2022 Published by Elsevier Ltd.
https://doi.org/10.1016/j.drudis.2022.103467This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Research in preclinical models and clinical studies has shown serum BDNF deficiency in major depression, with pharmacotherapy and electroconvulsive therapy (ECT) restoring its levels and activity [10–14], which correlates with the reversal of depression symptoms [15,16]. These findings are also of major interest for perinatal depression, given the symptomatic overlap with major depressive disorders and rising evidence for a reduction in BDNF level in the blood during pregnancy [17–23].

In this review, we explore the relationship between BDNF changes in peripheral circulation with female reproductive function and postpartum depression. We revisit the key facets of the biology of BDNF related to pregnancy and analyze clinical and preclinical data suggesting an association between BDNF deficiency and the disease. With the growing evidence for restoration of serum BDNF by antidepressant therapy, the emerging connection of depression with deficiency in this neurotrophin support its potential as a surrogate endpoint for preclinical and clinical studies of perinatal depression.

BDNF in the central nervous system and periphery

BDNF regulates a wide range of processes and mechanisms linked with neuronal development, differentiation, and synaptic plasticity, with its biology and functions in the normal and diseased nervous system extensively reviewed elsewhere [24–26]. In the central nervous system (CNS), BDNF is secreted mainly by neurons, astrocytes, and microglia [27] (Figure 1). Although typically considered as a neurotrophin acting on neurons via high-affinity TrkB receptor and low-affinity neurotrophin receptor p75 (p75NTR) [28–30], growing evidence suggest that the effects of BDNF extend beyond neuronal mechanisms and the nervous system, crossing blood–brain barriers (BBB) and acting at peripheral tissue and organs. Infusion of mature BDNF in the brain was shown to pass rapidly across the BBB into the peripheral circulation, at a rate similar to that of its absorption [31]. Although the mechanistic details remain unclear, this process appears to be mediated through saturable transport, is finely regulated, and might be altered in various diseases [32,33].

Most BDNF in peripheral circulation is derived from the CNS, with substantial amounts also secreted by peripheral cells, including megakaryocytes of bone marrow [34], endothelial cells [35,36], and immune cells (B and T lymphocytes, and monocytes) [37]. Most circulating BDNF is taken up in and stored by platelets, which release it upon demand [38,39] (Figure 1). The expression of p75NTR in B lymphocytes suggests paracrine effects of blood BDNF, with implications for humoral immunity [40]. BDNF is also present in T helper (Th) 1 and Th2 cells, with its activation of TrkB receptors of Th1 cells stimulating the release of cytokines (IFNγ and IL12). By contrast, the production of Th2 cytokines (IL4 and IL10) is nonresponsive to BDNF [41,42]. Overall, these observations suggest that BDNF produced in CNS can influence a variety of processes and functions at the periphery, whereas changes in its level in peripheral circulation can alter neural processes and mechanisms in the brain.

BDNF and female reproductive functions

Analysis of BDNF levels in the blood of different age groups and genders showed significant variations [43]. In healthy adults, the concentration of BDNF in serum was higher than in plasma, with most of it stored in platelets. During aging, BDNF concentration in the plasma of both men and women decreases, whereas the amount of BDNF stored in platelets remains stable. Measurements of BDNF in the plasma of adult men and women showed that, when matched for the age and weight, no differences could be detected. By contrast, the BDNF content in platelets was higher in men, irrespective of weight [43]. Assessment of BDNF variations during the menstrual cycle showed that its level in plasma peaks during the follicular and luteal phases, with concentrations falling during ovulation [44]. Differences were also reported in platelet BDNF levels between the first and second half of the menstrual cycle [45]. These alterations have been suggested to facilitate the onset of pregnancy, as well as the formation of the placenta, through effects of BDNF on trophoblast cells [46–48]. The expression of BDNF and TrkB receptors in the ovary, as well as its presence in the follicular fluid [49] and endometrium of the uterus [50], support its role in pregnancy and fetal development. Accordingly, reduced BDNF availability in follicular fluid in Val66Met BDNF gene polymorphisms appears to be associated with infertility and leads to poor outcomes of *in vitro* fertilization (IVF) treatment [51].

Although substantial data indicate that BDNF levels in the blood can be influenced by estrogen activity, the underlying mechanisms remain elusive. The positive correlation of BDNF and estradiol concentrations in the blood of nonpregnant women, with both peaking during the periovulatory period [52], implies that estrogen can positively regulate the BDNF level in the blood. Such interpretation agrees with the presence of a specific sequence homolog of estrogen response element in *BDNF* gene, which could mediate the effects of estrogen [53]. Estrogen can also indirectly influence the production of BDNF via activation of mitogen-activated protein kinase (MAPK) signaling, which promotes BDNF transcription through stimulation of cAMP-response element-binding protein (CREB) [54]. Regulation of peripheral BDNF by female gonad hormones is also supported by reports showing a reduction in its levels in amenorrhoeic women, whereas hormone replacement therapy has restorative effects [55,56]. Correlation studies of plasma BDNF with estradiol and progesterone also showed a positive association, with the gradual decline in gonad hormones during the onset of menopause linked with a reduction in BDNF activity [55].

The results of preclinical studies support the regulatory role of female gonad hormones, with BDNF transcription and translation significantly reduced in the brain of ovariectomized rats [57]. Given the key role of BDNF in influencing the mechanisms of cognition, memory, and mood [58], alterations in its level and activity related to variations in gonad hormones could contribute to subtle changes in mood and cognitive functions during the menstrual cycle [59,60]. However, with the onset of pregnancy, the relationship between estrogen and BDNF in peripheral circulation reverses, with a dramatic rise in blood estrogen paralleled by a decline in BDNF concentrations (Figure 1). As discussed below, the reduction in serum BDNF might contribute to pregnancy-related adjustments in neuronal and synaptic mechanisms, increasing the odds of developing depression.

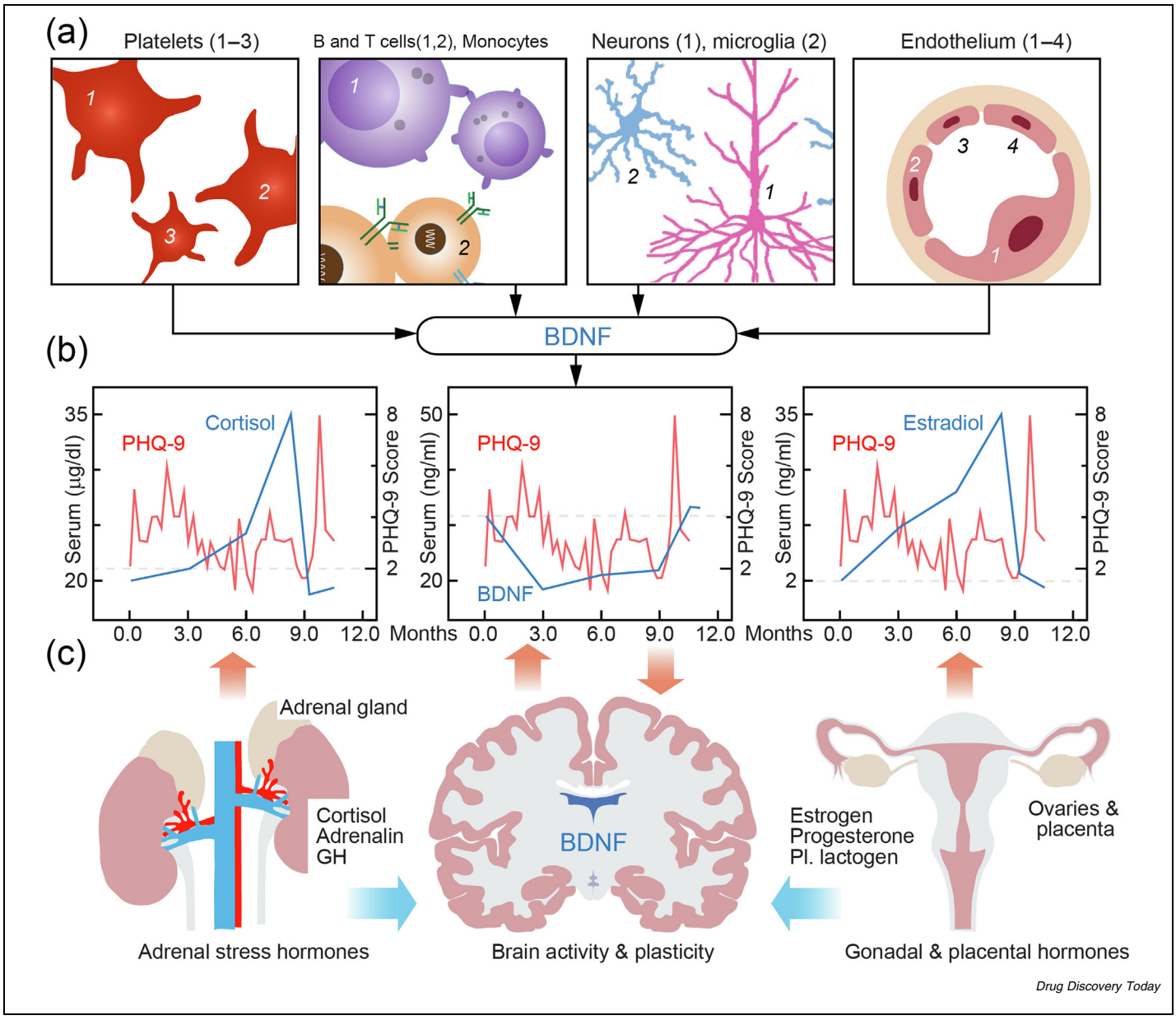

FIGURE 1

Brain-derived neurotrophic factor (BDNF) in peripheral circulation and its relationship with changes in stress and gonad hormones, and Patient Health Questionnaire 9 (PHQ-9) score of depression during pregnancy and early postpartum period. (a) Major cellular sources of peripheral (serum) BDNF. From left to right: platelets (1–3), B and T cells (1,2) and monocytes, neurons, and microglia (1,2) and endothelium (1–4, endothelial cells of a capillary). (b) Dynamics of serum cortisol [75], BDNF [76], and estradiol [77] concentrations and their relationship with PHQ-9 scores during pregnancy and after childbirth. PHQ-9 trace reproduced with permission from [78]. (c) Major players and interactions of BDNF, stress and sex hormones. Arrows indicate the direction of the flow of BDNF, cortisol, and estradiol. Abbreviations: GH, growth hormone, Pl, placental.

BDNF and perinatal depression: Clinical evidence

Analysis of BDNF changes in serum during pregnancy revealed its significant decline with recovery after childbirth [17,61]. Longitudinal measurements during the first, second, and third trimesters showed lower concentrations of BDNF, with complete recovery at 4–11 weeks postpartum [17]. During pregnancy, BDNF level in blood correlate positively with serotonin (5-HT), and negatively with dehydroepiandrosterone sulfate (DHEAS), estrogen, progesterone, and cortisol change [61].

Numerous questioners have been used to analyze the relationship between serum BDNF and perinatal depressive symptoms [20] (Table 1). Most of the reports found a significant association between the reduction in serum BDNF and risk of developing depression in pregnancy [18–22], as well as during the early postpartum period [17,63–66]. A cross-sectional antenatal study found lower BDNF by the 16th week of pregnancy correlated with risks of depression, although with no association observed with symptom intensity [18]. Two follow-up reports also found a decrease in serum BDNF linked with depression by the 16th gestational week [22] or earlier [62]. In a longitudinal analysis during pregnancy and 4–11 weeks postpartum, the association between BDNF and depression was only significant during the

TABLE 1

Summary of the relationship of BDNF concentration in peripheral circulation and results of depression test in clinical studies[a,b]

Subjects (*N*)	Age range	Depression test	Applied during	BDNF (ng/ml)	Measured during	Depression score–BDNF correlation	Refs
81	27–43	MADRS (+), EPDS (+)	II–III	1–17	PP	Negative	[19]
37	29.9 ± 2.2	EPDS (+)	PP	8.8	PP	Negative, BDNF lower versus EPDS (−)	[64]
303	28.5 ± 1.9	EPDS (–)	PP	14.3	PP	Negative, BDNF higher versus EPDS (+)	[64]
36	25 ± 6	BDI (+)	PP	1.8	PP	Negative, BDNF lower versus BDI (−)	[65]
36	25 ± 5	BDI (–)	PP	2.5	PP	Negative, BDNF higher versus BDI (+)	[65]
139	24.8 ± 4	CES-D (±)	III-PP	12–16	I–III, PP	Negative	[17]
40	20–40	EPDS (+)	III-PP	2.9	III–PP	Negative, BDNF lower versus EPDS (–)	[61]
40	20–40	EPDS (–)	III-PP	12.6	III–PP	Negative, BDNF higher versus EPDS (+)	[61]
29	19–35	MINI (+)	PP	2.08 ± 1.32	PP	Negative	[21]
161	19–35	MINI (−)	PP	2.28 ± 1.31	PP	No correlation	[21]
280	18–35	PHQ-9 (+)	I-III	17.08–24.20	I–III	Negative, BDNF lower versus PHQ-9 (–)	[18]
688	18–35	PHQ-9 (–)	I–III	17.37–25.85	I–III	Negative, BDNF higher versus PHQ-9 (+)	[18]
982	28.0 ± 6.2	PHQ-9 (±)	II–III	21.6 ± 6.3	II–III	Negative	[62]
58	Not specified	APGAR (+)	PP	199.45 ± 74.28	PP	Negative, BDNF lower versus APGAR (–)	[63]
45	Not specified	APGAR (–)	PP	259.4 ± 119.38	PP	Negative, BDNF higher versus APGAR (+)	[63]
25	29.08 ± 4.32	EPDI (+)	PP	193.56 ± 65.04	PP	Negative, BDNF lower versus EPDI (–)	[67]
93	27.25 ± 5.51	EPDI (–)	PP	229.04 ± 73.41	PP	Negative, BDNF higher versus EPDI (+)	[67]

[a] Tests used for scoring women for depression: APGAR, Appearance, Pulse, Grimace, Activity and Respiration; BDI, Beck's Depression Inventory; CES-D, Centre for Epidemiological Studies Depression; EPDI, Edinburgh Postnatal Depression Inventory; EPDS, Edinburgh Postnatal Depression Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; MINI, Mini International Neuropsychiatric Interview; PHQ-9, Patient Health Questionnaire 9. (+) and (–) indicate presence or absence of depression, respectively.

[b] Roman numerals indicate trimesters during pregnancy; PP, postpartum.

third trimester, with the onset of depression predicted by low BDNF level during the second trimester [17]. In addition to these reports, there were also studies showing weak trends of BDNF changes in pregnancy with depression [61] or no association [67] (Table 1).

Results of BDNF measurements after childbirth are consistent with the association between BDNF deficiency and risk of depression, with the level of the neurotrophin in the cord blood significantly lower in mothers with signs of depression compared with pregnant women without symptoms of depression [66]. Analysis of BDNF 24–48 h and 6 weeks postpartum also showed reduced BDNF levels in women with signs of depression [63]. A similar study collected serum 24–48 h after delivery, with 3 months follow-up, and showed that, in women who met criteria for postpartum depression, BDNF was lower compared with those without signs of depression [64]. Based on analysis of the threshold level of BDNF decline associated with the onset of postpartum depression, the authors proposed 12.0 ng/ml as a cut-off point [64]. Gazal and coworkers studied correlation of changes in BDNF with the severity of depression between 30 and 90 days postpartum, with BDNF concentrations negatively correlating with Beck Depression Inventory (BDI) scores [65] (Table 1). There have been also reports of no association between BDNF levels and depression at 6 weeks postpartum [68]. Of note, the association between depression and BDNF appears to be specific to mothers, because assessment of BDNF in fathers screened positive for perinatal depression (paternal) revealed no changes [19].

Given the role of BDNF in placental growth and ~twofold higher numbers of delivery of low birth-weight (LBW) infants in Black women, Christian and colleagues investigated the relationship between BDNF, depressive symptoms, and race [17]. In all tested women, serum BDNF declined from the first through the third trimester of pregnancy and recovered after childbirth, with its levels in the blood of Black women exceeding those of White women during the first trimester, second trimester, and postpartum period. Importantly, women delivering LBW infants showed significantly lower levels of serum BDNF during the third trimester, irrespective of race. Perinatal BDNF deficiency has been also linked with gestational abnormalities, such as preterm birth (PTB), intrauterine growth restriction (IUGR), and LBW [17,69]. Whether there is an association between these conditions and perinatal depression remains to be shown.

BDNF and depression in preclinical models

Animal models have been increasingly used for studies of perinatal depression, which not only allow measurements of neuroendocrine and behavioral changes, but can also be used for specific tests to gain mechanistic insights. By combining genetic, pharmacological, and behavioral studies, it was reported that Val66-Met SNP homozygote mice with reduced BDNF availability showed increased anxiety-like behaviors over the prepubertal period and early adulthood, as well as during the estrus phase [70]. Analysis of the effects of expressional changes of the TrkB receptor in the brain of ovariectomized rats with and without supplementation of the estrogen precursor dehydroepiandrosterone (DHEA) for 12 weeks revealed that DHEA (and estradiol) increased TrkB expression and ameliorated depression symptoms in sucrose preference and locomotor activity tests [56]. Behavioral trials in mice at 28 days postpartum exposed to stress during their first week of gestation, followed by immunohistochemical analysis, demonstrated that gestational stress lowered the level of hippocampal BDNF, without changing TrkB immunostaining [71]. The expression of the p11 protein, which is controlled by BDNF, was also decreased in the hippocampus of this model. In the forced swim, tail suspension and elevated plus-maze paradigms, Zhang and coworkers reported that, in ovariectomized adult mice primed in hormone-simulated pregnancy (HSP), with-

drawal of estradiol benzoate (EB) caused depression-like symptoms, an effect that was not observed in mice maintained on EB [72]. Of note, BrdU staining of the hippocampal dentate area of EB mice showed enhanced adult neurogenesis in the EB group, whereas, in estrogen-withdrawal (EW) mice, the number of BrdU neurons was reduced. In both EW and OVX mice, BDNF expression was also reduced compared with HSP and control groups [72]. Another study in EW rats suggested that depression is linked with enhanced galanin activity, with the expression of GALR1 (but not GALR2/3) upregulated in the prefrontal cortex (PFC) [73]. Silencing GALR1 by small interfering (si)RNA injected bilaterally in PFC ameliorated signs of depression, an effect associated with the downregulation of CREB-BDNF expression and reduction in 5-HT levels in the PFC. These findings imply a complex interplay between BDNF, GALR1, and 5-HT signaling in the PFC of rats with EW-induced depression [73]. The role of BDNF and TrkB signaling in the onset of depression is also supported by the results of repeated restrain experiments in pregnant rats, showing increased levels of adrenocorticotrophic hormone (ACTH) and corticosterone in the blood, and a reduction in BDNF and TrkB expression in the hippocampus [74]. The authors speculated that a pregnancy-related decrease in BDNF level and suppression of TrkB signaling might contribute to the development of depression-like behavior.

Concluding remarks and outlook

Perinatal depression, which sets off during pregnancy or within 6–8 weeks after childbirth, is the most common cause of the admission of women to a psychiatric unit. The arrival of the disease at this crucial time can have detrimental impact on the ability of mothers to relate, respond, and care for their infants, thwarting the evolving maternal–infant relationship. Despite high prevalence, screening for perinatal depression is not part of routine examinations during pregnancy, to a large extent because of the lack of rapid and specific tests. The standard diagnosis based on questionnaires comes with limited predictive value and risk of false positives. With high incidents of neglected cases of perinatal depression and concerns over stigma associated with diagnosis of mental disorders, there is major need for cost-effective and high predictive value biomarkers. As discussed throughout this article, there is increasing clinical and preclinical evidence suggesting a significant association between serum BDNF deficiency and the risk of developing perinatal depression. Although the role of physiological decline of BDNF during pregnancy remains to be determined, given the potent effects BDNF on multiple key aspects of neuronal biology and synaptic functions, it is hardly surprising that its reduction in pregnancy is associated with high incidents of depression. With increasing evidence for restorative effects of antidepressants on BDNF levels in the blood and its key role in controlling neurobiological mechanisms involved in depression, the strengthening link of BDNF deficiency and depression in pregnant women advocates the potential use of changes in this neurotrophin as a surrogate endpoint for clinical and preclinical studies.

Authors' contributions

S.S., E.D., K.Y., and S.V.O. prepared the first draft of the manuscript. All authors contributed to several revisions of the material, including the final version. R.P., E.D., and S.V.O. prepared the illustrative materials and tables. All authors have read and approved the submission version of the manuscript.

Data availability

No data was used for the research described in the article.

Acknowledgments

E.D. received support from the Slovak Research and Development Agency Grant (APVV-19-0435 and APVV-20-0202) and Research Grant Agency of the Ministry of Education, Science, Research and Sport, and Slovak Academy of Sciences grant (Grant VEGA-2/0057/22). K.Y. received support from the Republic of Armenia State Committee of Science (20TTCG-3A012 and N 10-14/I-1) and the European Union-funded H2020 COBRAIN project (857600). S.V.O. acknowledges the Innovation Fund Award and Research Excellent Framework Program. The authors thank E. Smirnova for the assistance with the preparation of illustrative material.

Declaration of interests

The authors report no potential conflict of interest.

References

[1] Soma-Pillay, P. *et al.* (2016) Physiological changes in pregnancy. *Cardiovasc. J. Afr.* 27, 89–94.
[2] Kaaja, R.J. and Greer, I.A. (2005) Manifestations of chronic disease during pregnancy. *J. Am. Med. Assoc.* 294, 2751–2757.
[3] Meltzer-Brody, S. *et al.* (2018) Postpartum psychiatric disorders. *Nat. Rev. Dis. Primers* 4, 18022.
[4] Sadock, B.J. *et al.* (2007) *Kaplan & Sadock's Synopsis Of Psychiatry: Behavioral Sciences/Clinical Psychiatry* (10th ed), Wolter Kluwer/Lippincott Williams & Wilkins.
[5] Field, T. (2017) Prenatal depression risk factors, developmental effects and interventions: a review. *J. Pregnancy Child Health.* 4, 301.
[6] Ghaedrahmati, M. *et al.* (2017) Postpartum depression risk factors: A narrative review. *J. Educ. Health Promot.* 6, 60.
[7] Zheleznyakova, G.Y. *et al.* (2016) BDNF DNA methylation changes as a biomarker of psychiatric disorders: literature review and open access database analysis. *Behav. Brain Funct.* 12, 17.
[8] Peng, S. *et al.* (2018) BDNF as a biomarker in diagnosis and evaluation of treatment for schizophrenia and depression. *Discov. Med.* 26, 127–136.
[9] Polyakova, M. *et al.* (2015) BDNF as a biomarker for successful treatment of mood disorders: a systematic & quantitative meta-analysis. *J. Affect. Disord.* 174, 432–440.
[10] Pelosof, R. *et al.* (2022) BDNF blood levels after electroconvulsive therapy in patients with mood disorders: an updated systematic review and meta-analysis. *World J. Biol. Psychiatry* DOI: 10.1080/15622975.2022.2058083 (Published online April 21, 2022).
[11] Sorri, A. *et al.* (2018) Effect of electroconvulsive therapy on brain–derived neurotrophic factor levels in patients with major depressive disorder. *Brain Behav.* 8, e01101.
[12] Lakshminarasimhan, H. and Chattarji, S. (2012) Stress leads to contrasting effects on the levels of brain derived neurotrophic factor in the hippocampus and amygdala. *PLoS One* 7, e30481.

[13] Jha, S. *et al.* (2016) Antidepressive and BDNF effects of enriched environment treatment across ages in mice lacking BDNF expression through promoter IV. *Transl. Psychiatry* 6, e896.
[14] Dremencov, E. Jezova, D. Barak, S. Gaburjakova, J. Gaburjakova, M. Kutna, V. and Ovsepian, S.V. (2021) Trophic factors as potential therapies for treatment of major mental disorders. *Neurosci Lett.* 764. DOI: 10.1016/j.neulet.2021.136194 136194.
[15] Castren, E. and Antila, H. (2017) Neuronal plasticity and neurotrophic factors in drug responses. *Mol. Psychiatry* 22, 1085–1095.
[16] Zhou, C. *et al.* (2017) Meta-analyses of comparative efficacy of antidepressant medications on peripheral BDNF concentration in patients with depression. *PLoS One* 12, e0172270.
[17] Christian, L.M. *et al.* (2016) Serum brain-derived neurotrophic factor (BDNF) across pregnancy and postpartum: associations with race, depressive symptoms, and low birth weight. *Psychoneuroendocrinology* 74, 69–76.
[18] Fung, J. *et al.* (2015) Association of decreased serum brain-derived neurotrophic factor (BDNF) concentrations in early pregnancy with antepartum depression. *BMC Psychiatry* 15, 43.
[19] Kittel-Schneider, S. *et al.* (2022) A pilot study of multilevel analysis of BDNF in paternal and maternal perinatal depression. *Arch. Womens Ment. Health* 25, 237–249.
[20] Mandolini, G.M. *et al.* (2020) Association between serum BDNF levels and maternal perinatal depression: a review. *J. Affect. Disord.* 261, 271–276.
[21] Pinheiro, R.T. *et al.* (2012) Brain-derived neurotrophic factor levels in women with postpartum affective disorder and suicidality. *Neurochem. Res.* 37, 2229–2234.
[22] Yang, N. *et al.* (2016) Serum brain-derived neurotrophic factor (BDNF) concentrations in pregnant women with post-traumatic stress disorder and comorbid depression. *Arch. Womens Ment. Health* 19, 979–986.
[23] Yang, T. *et al.* (2020) The role of BDNF on neural plasticity in depression. *Front. Cell. Neurosci.* 14, 82.
[24] Hong, C.J. *et al.* (2011) Effects of BDNF polymorphisms on brain function and behavior in health and disease. *Brain Res. Bull.* 86, 287–297.
[25] Li, Y. *et al.* (2022) The role of brain derived neurotrophic factor in central nervous system. *Front. Aging Neurosci.* 14 986443.
[26] Lu, B. *et al.* (2013) BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases. *Nat. Rev. Neurosci.* 14, 401–416.
[27] Brigadski, T. and Lessmann, V. (2020) The physiology of regulated BDNF release. *Cell Tissue Res.* 382, 15–45.
[28] Chao, M.V. and Bothwell, M. (2002) Neurotrophins: to cleave or not to cleave. *Neuron* 33, 9–12.
[29] Squinto, S.P. *et al.* (1991) trkB encodes a functional receptor for brain-derived neurotrophic factor and neurotrophin-3 but not nerve growth factor. *Cell* 65, 885–893.
[30] Chao, M.V. (1994) The p75 neurotrophin receptor. *J. Neurobiol.* 25, 1373–1385.
[31] Pan, W. *et al.* (1998) Transport of brain-derived neurotrophic factor across the blood-brain barrier. *Neuropharmacology* 37, 1553–1561.
[32] Lesniak, A. *et al.* (2021) Loss of brain-derived neurotrophic factor (BDNF) resulting from congenital- or mild traumatic brain injury-induced blood-brain barrier disruption correlates with depressive-like behaviour. *Neuroscience* 458, 1–10.
[33] Xu, G. *et al.* (2019) Restraint stress induced hyperpermeability and damage of the blood–brain barrier in the amygdala of adult rats. *Front. Mol. Neurosci.* 12, 32.
[34] Chacon-Fernandez, P. *et al.* (2016) Brain-derived neurotrophic factor in megakaryocytes. *J. Biol. Chem.* 291, 9872–9881.
[35] Grasman, J.M. and Kaplan, D.L. (2017) Human endothelial cells secrete neurotropic factors to direct axonal growth of peripheral nerves. *Sci. Rep.* 7, 4092.
[36] Nakahashi, T. *et al.* (2000) Vascular endothelial cells synthesize and secrete brain-derived neurotrophic factor. *FEBS Lett.* 470, 113–117.
[37] Kerschensteiner, M. *et al.* (1999) Activated human T cells, B cells, and monocytes produce brain-derived neurotrophic factor *in vitro* and in inflammatory brain lesions: a neuroprotective role of inflammation? *J. Exp. Med.* 189, 865–870.
[38] Fujimura, H. *et al.* (Apr 2002) Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation. *Thromb. Haemost.* 87, 728–734.
[39] Serra-Millas, M. (2016) Are the changes in the peripheral brain-derived neurotrophic factor levels due to platelet activation? *World J. Psychiatry* 6, 84–101.
[40] Delivanoglou, N. *et al.* (2020) Spatio-temporal expression profile of NGF and the two-receptor system, TrkA and p75NTR, in experimental autoimmune encephalomyelitis. *J. Neuroinflammation* 17, 41.
[41] Besser, M. and Wank, R. (1999) Cutting edge: clonally restricted production of the neurotrophins brain-derived neurotrophic factor and neurotrophin-3 mRNA by human immune cells and Th1/Th2-polarized expression of their receptors. *J. Immunol.* 162, 6303–6306.
[42] Yap, N.Y. *et al.* (2021) Relationship between cytokines and brain-derived neurotrophic factor (BDNF) in trajectories of cancer-related cognitive impairment. *Cytokine* 144 155556.
[43] Lommatzsch, M. *et al.* (2005) The impact of age, weight and gender on BDNF levels in human platelets and plasma. *Neurobiol. Aging* 26, 115–123.
[44] Cubeddu, A. *et al.* (2011) Brain-derived neurotrophic factor plasma variation during the different phases of the menstrual cycle in women with premenstrual syndrome. *Psychoneuroendocrinology* 36, 523–530.
[45] Bódis, J. *et al.* (2014) Platelet-associated regulatory system (PARS)' with particular reference to female reproduction. *J. Ovarian Res.* 7, 55.
[46] Kawamura, K. *et al.* (2009) Brain-derived neurotrophic factor promotes implantation and subsequent placental development by stimulating trophoblast cell growth and survival. *Endocrinology* 150, 3774–3782.
[47] Mayeur, S. *et al.* (2010) Placental BDNF/TrkB signaling system is modulated by fetal growth disturbances in rat and human. *Placenta* 31, 785–791.
[48] Chow, R. *et al.* (2020) Brain-derived neurotrophic factor (BDNF) expression and function in the mammalian reproductive Tract. *Hum. Reprod. Update* 26, 545–564.
[49] Streiter, S. *et al.* (2016) The importance of neuronal growth factors in the ovary. *Mol. Hum. Reprod.* 22, 3–17.
[50] Anger, D.L. *et al.* (2007) Tyrosine receptor kinase B (TrkB) protein expression in the human endometrium. *Endocrine* 31, 167–173.
[51] Zhang, Q.Y. *et al.* (2012) BDNF Val66Met polymorphism is associated with Stage III-IV endometriosis and poor *in vitro* fertilization outcome. *Hum. Reprod.* 27, 1668–1675.
[52] Monteleone, P. *et al.* (2007) Brain derived neurotrophic factor circulating levels in patients undergoing IVF. *J. Assist. Reprod. Genet.* 24, 477–480.
[53] Sohrabji, F. *et al.* (1995) Identification of a putative estrogen response element in the gene encoding brain-derived neurotrophic factor. *PNAS* 92, 11110–11114.
[54] Scharfman, H.E. and Maclusky, N.J. (2005) Similarities between actions of estrogen and BDNF in the hippocampus: coincidence or clue? *Trends Neurosci.* 28, 79–85.
[55] Begliuomini, S. *et al.* (2007) Influence of endogenous and exogenous sex hormones on plasma brain-derived neurotrophic factor. *Hum. Reprod.* 22, 995–1002.
[56] Wu, S. *et al.* (2020) Long-term supplementation of dehydroepiandrosterone improved depressive-like behaviors by increasing BDNF expression in the hippocampus in ovariectomized rats. *Heliyon* 6, e05180.
[57] Singh, M. *et al.* (1995) The effect of ovariectomy and estradiol replacement on brain-derived neurotrophic factor messenger ribonucleic acid expression in cortical and hippocampal brain regions of female Sprague-Dawley rats. *Endocrinology* 136, 2320–2324.
[58] McEwen, B.S. and Milner, T.A. (2017) Understanding the broad influence of sex hormones and sex differences in the brain. *J. Neurosci. Res.* 95, 24–39.
[59] Farage, M.A. *et al.* (2008) Cognitive, sensory, and emotional changes associated with the menstrual cycle: a review. *Arch. Gynecol. Obstet.* 278, 299–307.
[60] Sacher, J. *et al.* (2013) Evidence from neuroimaging for the role of the menstrual cycle in the interplay of emotion and cognition. *Front. Hum. Neurosci.* 7, 374.
[61] Lommatzsch, M. *et al.* (2006) Maternal serum concentrations of BDNF and depression in the perinatal period. *Psychoneuroendocrinology* 31, 388–394.
[62] Yang, N. *et al.* (2017) Correlates of early pregnancy serum brain-derived neurotrophic factor in a Peruvian population. *Arch. Womens Ment. Health* 20, 777–785.
[63] Dhiman, P. *et al.* (2014) Association of foetal APGAR and maternal brain derived neurotropic factor levels in postpartum depression. *Asian J. Psychiatr.* 11, 82–83.
[64] Gao, X. *et al.* (2016) Serum BDNF concentration after delivery is associated with development of postpartum depression: a 3-month follow up study. *J. Affect. Disord.* 200, 25–30.
[65] Gazal, M. *et al.* (2012) Brain-derived neurotrophic factor in post-partum depressive mothers. *Neurochem. Res.* 37, 583–587.
[66] Sonmez, E.O. *et al.* (2019) Effect of maternal depression on brain-derived neurotrophic factor levels in fetal cord blood. *Clin. Psychopharmacol. Neurosci.* 17, 308–313.
[67] Akbaba, N. *et al.* (2018) Neurotrophins and neuroinflammation in fetuses exposed to maternal depression and anxiety disorders during pregnancy: a comparative study on cord blood. *Arch. Womens Ment. Health* 21, 105–111.
[68] Guintivano, J. *et al.* (2018) Adverse life events, psychiatric history, and biological predictors of postpartum depression in an ethnically diverse sample of postpartum women. *Psychol. Med.* 48, 1190–1200.

[69] Malamitsi-Puchner, A. *et al*. (2006) Intrauterine growth restriction, brain-sparing effect, and neurotrophins. *Ann. N. Y. Acad. Sci.* 1092, 293–296.
[70] Bath, K.G. *et al*. (2012) Variant brain-derived neurotrophic factor (Valine66Methionine) polymorphism contributes to developmental and estrous stage-specific expression of anxiety-like behavior in female mice. *Biol. Psychiatry* 72, 499–504.
[71] Vanmierlo, T. *et al*. (2018) Gestational stress in mouse dams negatively affects gestation and postpartum hippocampal BDNF and P11 protein levels. *Mol. Cell. Neurosci.* 88, 292–299.
[72] Zhang, Z. *et al*. (2016) Postpartum estrogen withdrawal impairs hippocampal neurogenesis and causes depression- and anxiety-like behaviors in mice. *Psychoneuroendocrinology* 66, 138–149.
[73] Li, H. *et al*. (2018) Inhibition of GALR1 in PFC alleviates depressive-like behaviors in postpartum depression rat model by upregulating CREB-BNDF and 5-HT levels. *Front. Psych.* 9, 588.
[74] Maghsoudi, N. *et al*. (2014) Effect of chronic restraint stress on HPA axis activity and expression of BDNF and Trkb in the hippocampus of pregnant rats: possible contribution in depression during pregnancy and postpartum period. *Basic Clin. Neurosci.* 5, 131–137.
[75] Osayande, O.E. *et al*. (2017) Serum cortisol levels in pregnancy and six weeks postpartum. *Afr. Scientist* 18, 235–238.
[76] Garcés, M.F. *et al*. (2014) Brain-derived neurotrophic factor is expressed in rat and human placenta and its serum levels are similarly regulated throughout pregnancy in both species. *Clin. Endocrinol.* 81, 141–151.
[77] Grattan, D.R. and Ladyman, S.R. (2020) Neurophysiological and cognitive changes in pregnancy. *Handb. Clin. Neurol.* 171, 25–55.
[78] Hu, M. *et al*. (2022) The prevalence and correlates of peripartum depression in different stages of pregnancy during COVID-19 pandemic in China. *BMC Pregnancy Childbirth* 22, 114.