Selective serotonin reuptake inhibitor effects on neural biomarkers of perinatal depression

Jodi L Pawluski, Ursula Brain, Geoffrey L Hammond, Tim F Oberlander

Selective Serotonin Reuptake Inhibitor Effects on Neural Biomarkers of Perinatal Depression

(Short Communication)

Jodi L. Pawluski[1*], Ursula Brain[2], Geoffrey L. Hammond[3] and Tim F. Oberlander[2]

[1]Univ Rennes, Inserm, EHESP, Irset (Institut de Recherche en Santé, Environnement et Travail), UMR_S 1085, F-35000 Rennes, France

[2]Department of Pediatrics, The University of British Columbia, BC Children's Hospital, 4480 Oak Street, Vancouver, BC, V6H 3V4, Canada

[3]Department of Cellular and Physiological Sciences, Faculty of Medicine, The University of British Columbia, Vancouver, Canada

***Corresponding Author:** Jodi L. Pawluski, Ph.D., Université de Rennes 1, Irset-Inserm U1085, Campus Villejean, 9 avenue du Prof. Leon Bernard, 35000 Rennes, FRANCE, Phone: +33(0)2 23.23.41.90, Email : j.pawluski@gmail.com / Jodi-lynn.pawluski@univ-rennes1.fr . ORCID iD 0000-0002-8240-8178

Summary

The effect of perinatal Selective Serotonin Reuptake Inhibitors (SSRIs) on brain-derived neurotrophic factor (BDNF) and S100 calcium binding protein B (S100B), has not been investigated. Using a cohort of 86 pregnant women, we found that SSRIs significantly increase BDNF levels in late pregnancy and that S100B, but not BDNF, is associated with maternal

depression in SSRI-treated women only. This shows that serum S100B could be a unique biomarker to determine efficacy of SSRIs during gestation.

Key words: depression; anxiety; antidepressants; gestation; motherhood; neuroplasticity

Introduction

Our understanding and use of biomarkers that reflect the pathophysiology of maternal depression remains limited. Serum brain-derived neurotrophic factor (BDNF) has been proposed as a biomarker for perinatal depression (Christian et al. 2016; Gao et al. 2016)(Guintivano et al. 2017). BDNF is a neurotrophin involved in neuroplasticity and implicated in the pathophysiology and treatment of mood disorders (Castren et al. 2007): with lower serum BDNF levels being associated with depression (aan het Rot et al. 2009). Similarly, during the perinatal period, low serum BDNF levels are associated with increased 3rd trimester depressive symptoms (Christian et al. 2016) and serum BDNF levels are significantly lower in women with postpartum depression (Gao et al. 2016; Lommatzsch et al. 2006). Recent research in rodent models has also shown that gestational stress can reduce levels of BDNF in the hippocampus of the mother (Vanmierlo et al. 2018).

Selective serotonin reuptake inhibitors (SSRIs) are the treatment of choice for perinatal depression and are prescribed to up to 10% of pregnant women (Oberlander et al. 2006; Pawluski et al. 2017). These medications can act, in part, by increasing BDNF levels, which can alleviate depression symptoms by their actions in the brain (aan het Rot et al. 2009; Gupta et al. 2017). Serum BDNF levels are positively correlated with serum 5-hydroxytryptamine (5-HT) levels during gestation and the postpartum period (Lommatzsch et al. 2006). However, the impact of SSRIs on BDNF during the perinatal period has not been assessed.

Recent attention has turned to S100 calcium-binding protein B (S100B) as another biomarker of perinatal depression in women (Pawluski et al. 2009). The production of S100B by astrocytes is regulated by serotonin and is involved in the outgrowth and survival of neurons and the stimulation of glial cell proliferation. In SSRI-treated women, serum S100B levels are elevated but it is not known how S100B is related to maternal mood (Bellissima et al. 2015; Pawluski et al. 2009). We therefore sought to determine how perinatal SSRIs influence maternal serum BDNF and S100B levels during late pregnancy and at delivery and how changes in serum levels of these factors might be related to maternal depressive and anxiety symptoms.

Materials and Methods

Subjects. Maternal serum samples were obtained for analysis of BDNF and S100B from a cohort (*n*=86) of mothers recruited in their early second trimester to participate in a study of psychotropic medication use during the perinatal period. This was done with approval from The

University of British Columbia Research Ethics Board, Children's and Women's Health Centre of British Columbia Research Review Committee, and informed consent. For the present study serum BDNF and S100B levels were assayed from SSRI treated (n=22-25) and non-SSRI treated (n=33-38) women during late gestation and at delivery. Non-SSRI treated women were considered healthy controls. However, mood symptoms were assessed in all participants during the study. This subset of women chosen was based on serum availability for analysis.

None of the mothers took other serotonergic medications during their pregnancies. In the SSRI-treated group, 4 women also took another antidepressant medication and 5 women were also prescribed an antipsychotic. Women in the treated group were on SSRIs for an average of 261.07 ± 44.19 (range 94-290) days and, except for 2 women, all women in the SSRI -treated group were on medication for at least 247 days of gestation and all continued SSRI medication up to the time of delivery. Outcomes were compared with mothers not using any medication. Mode of delivery was recorded (vaginal versus C-section). Neonatal outcomes were tabulated from the immediate newborn period. Apgar scores at 1 and 5 minutes, sex, birth weight, head circumference, body length and gestational age were obtained. Only Apgar scores at 1 minutes and gestational age were different between SSRI-exposed and non-exposed neonates where lower Apgar scores at 1 minute and slightly younger gestational ages were evident (Pawluski et al 2012). Demographic information and neonatal characteristics from this cohort of mothers has been published and details can be found there (Pawluski et al. 2012).

Maternal Mood. During pregnancy, maternal anxiety and depression were assessed at the time of study enrollment (approximately 26–28 weeks) and again at 36 weeks gestation (36.2 ± 0.7 weeks). *The Hamilton Rating Scale for Depression (HAMD), The Hamilton Rating Scale for Anxiety (HAMA*), and *the Edinburgh Postnatal Depression Scale (EPDS)* were used. Self-reported history of depression or anxiety was also asked of each participant at the first visit.

Serum BDNF and S100B analysis. Blood samples were collected at 36 weeks gestation, serum samples were taken at 8 am, 2.5 hours before SSRI medication was taken. Delivery blood samples were taken at term and up to 2 hours after delivery of the placenta from the ante cubital fossa (arm). 33-38 samples of non-SSRI treated women and 22-25 samples of SSRI-treated

women were assessed at 36 weeks gestation and delivery. Samples were centrifuged at 1,300*g* for 8 minutes at 4 ºC. Serum was collected and stored at -80 ºC until analysis.

Serum samples were analyzed in duplicate using a commercially available ELISA kits for BDNF (Human BDNF, R&D systems, #DBD00, USA) and S100B (Human S100B ELISA, BioVendor, #RD192090100R,Czech Republic). The sensitivity was estimated to be 20pg/ml for the BDNF assay and 15pg/ml for the S100B assay. Average intra-assay and inter-assay coefficients of variation were less than 10%. The majority of S100B levels at 36 weeks gestation were below the detection limit so only S100B levels from delivery were used for analyses.

Statistical analysis. Using Statistica 64 (Dell Inc) software analysis of variance tests (ANOVAs) were calculated on maternal mood symptoms and serum levels of BDNF or S100B levels as a within-subjects factor and treatment (SSRI treated, non-SSRI treated) as a between-subjects factor. An analysis of covariance (ANCOVA) was performed on BDNF and S100B levels using measures of maternal mood (HAMD) and mode of delivery and neonatal characteristics (Apgar scores at 5 min, gestational age, etc), as well as maternal BMI and ethnicity as covariates. Both maternal BMI and ethnicity are known to affect BDNF levels (Ben Abdesselam et al. 2003; Christian et al. 2016; Lommatzsch et al. 2006; Lommatzsch et al. 2005). Chi-square tests were computed for self-reported history of depression or anxiety between groups. Pearson correlations were conducted between maternal mood scores (HAMD), maternal BDNF and S100B levels in SSRI treated and non-treated women. Pearson correlations were also conducted on maternal measures of affective symptoms in the HAMD, HAMA, and EPDS. Linear regression models were also computed to assess the contribution of multiple factors on the correlations (such as mode of delivery, gestational length, maternal mood scores, duration of SSRI use during pregnancy). Significance was set a $p < 0.05$.

Results

The HAMD, HAMA, and EPDS scores were significantly positively correlated (r's=.55-.85, p's=0.00), thus to avoid redundancy HAMD scores were used throughout as our focus was on mood symptoms (HAMA assesses anxiety and the EPDS assesses both depression and anxiety (Rowe et al. 2008; Tuohy and McVey 2008)). The SSRI treated women at 36 weeks gestation had significantly higher HAMD scores compared to non-SSRI treated women (F(1,

61)=5.43, p=.02, Table 1). SSRI-treated women were significantly more likely than non-SSRI treated women to self-report a history of depression (chi^2=46.33, p=0.00001) and anxiety (chi^2=11.64, p=0.0006; Table 1). Eighty-three percent of the participants identified as being white and there were no significant differences between groups in ethnic diversity (p=0.5). SSRI-treated women had a significantly higher BMI at 36wks gestation (F(1, 82)=6.3602, p=.01, 27.4±3.7 for non-treated and 29.9±5.4 for SSRI-treated).

Women prescribed SSRIs had significantly higher serum levels of BDNF at 36 weeks gestation (F(1, 59)=5.7386, p=.02, controlling for BMI and ethnicity, Figure 1A). Furthermore, lower BDNF levels at delivery were marginally associated with increased maternal depressed symptoms during late gestation (36weeks) in non-SSRI treated women (Pearson correlation: r=-.32, p=0.058) but not SSRI treated (Pearson correlation: r=.07, p=.77, Figure 1B).

Lower S100B levels at delivery were significantly associated with higher maternal depression symptoms in SSRI-treated women (Pearson correlation: r=-.62, p = 0.003, regardless of BMI or ethnicity; Figure 1C) and there was no relationship between S100B and maternal mood symptoms in non-SSRI treated women (Pearson correlation: r=-.13, p=.47). There were no other significant differences between groups.

Discussion

In the present cohort SSRI-treated women had increased depression symptoms at 36 weeks gestation compared to non-SSRI treated women. Both SSRI-treated and non-treated pregnant women showed a wide range in symptoms of depression which allowed for investigation of the association between serum biomarkers and depressive symptoms. Our main findings show that in SSRI-treated women there is a significant increase in serum BDNF levels during late pregnancy which is in line with previous work showing the BDNF is associated with increased 5HT during in the peripartum period (Lommatzsch et al. 2006). This finding also expands previous work in non-pregnant individuals showing a positive association between antidepressant medications and serum BDNF levels (Duman and Monteggia 2006). How increased levels of serum BDNF with SSRIs translate to changes in neurochemistry and neural activity in the maternal brain remain to be determined.

It has been reported that serum BDNF levels are negatively associated with perinatal depressive symptoms and maternal stress (Christian et al. 2016; Gao et al. 2016; Lommatzsch et

al. 2006; Vanmierlo et al. 2018). In the present study this relationship was not evident in SSRI-treated pregnant women suggesting that the increase in BDNF with SSRI-treatment is not acting to alleviate depressive symptoms and that BDNF is not a biomarker of depressive-symptoms in women prescribed SSRIs during pregnancy. As with previous reports showing a negative relationship between serum BDNF levels and perinatal depression (Christian et al. 2016; Gao et al. 2016), we do show a marginal negative correlation between serum BDNF levels and depressive symptoms during late pregnancy, but in non SSRI-treated women only.

When looking at serum S100B levels we found that SSRI-treated women have a significant negative correlation between serum S100B levels and maternal mood scores. Serotonin can increase S100B levels (Whitaker-Azmitia et al. 1990) and S100B is known to alleviate depressive-like symptoms via its actions on the 5-HT7 receptor (Stroth and Svenningsson 2015), thus it may be that the increase in serotonin activity at the synaptic cleft, after SSRI treatment, increases S100B and decreases symptoms of depression via actions on the 5-HT7 receptor.

Conclusion

Taken together, this work points a significant role of SSRIs on neuro-biomarkers of maternal depressive symptoms during the perinatal period. This work also shows that S100B may be a unique biomarker for determining the efficacy of SSRIs in treating maternal affective disorders during gestation. Further work is needed to determine the direct neurobiological effects of SSRIs on the maternal brain.

178 **Figure legend**

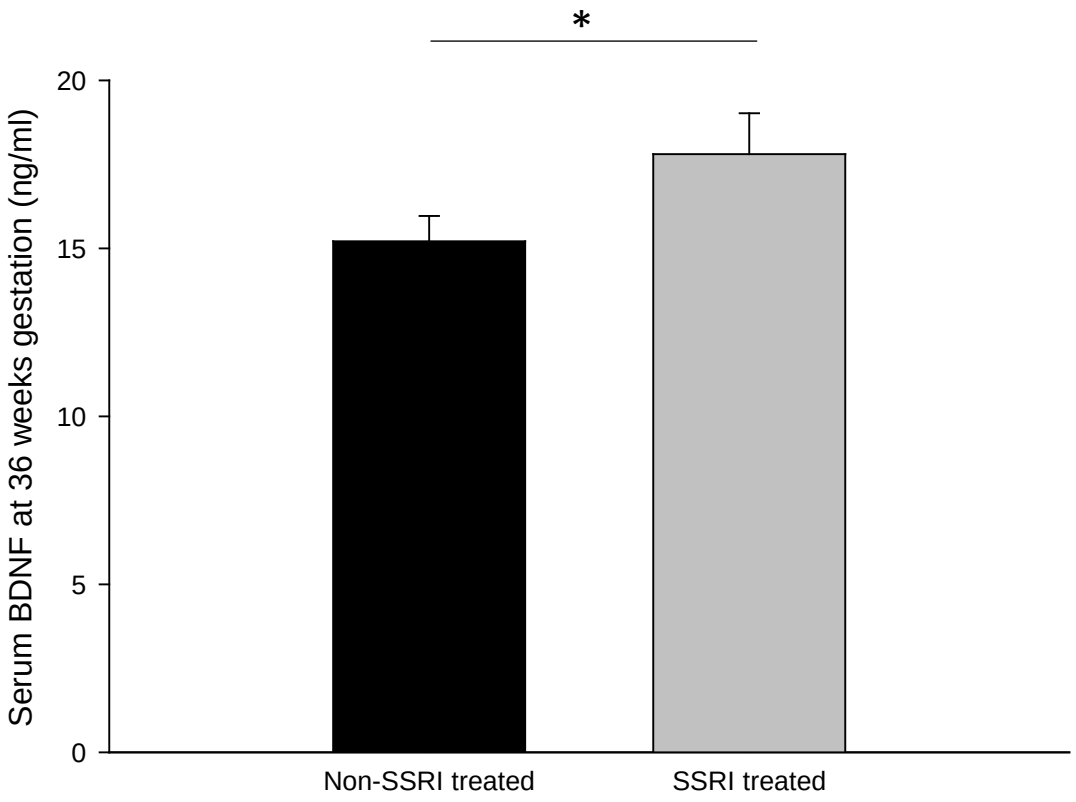
179

180 **Figure 1.** Serum biomarkers (S100B and BDNF) and maternal depression symptoms in SSRI
181 treated and non-SSRI treated women. A) Mean (±SEM) serum BDNF levels at 36 weeks
182 gestation ($F(1, 59)=5.7$, $p=.02$). B) Correlations between serum BDNF levels at delivery and
183 maternal depression symptoms (non-SSRI treated women $r=-.32$, $p=0.058$; SSRI treated women
184 $r=.07$, $p=.77$). C) Correlations between serum S100B levels at delivery and maternal depression
185 symptoms (non-SSRI treated women $r=-.13$, $p=.47$; SSRI-treated women $r=-.62$, $p = 0.003$).
186 *denotes significance $p<0.05$.

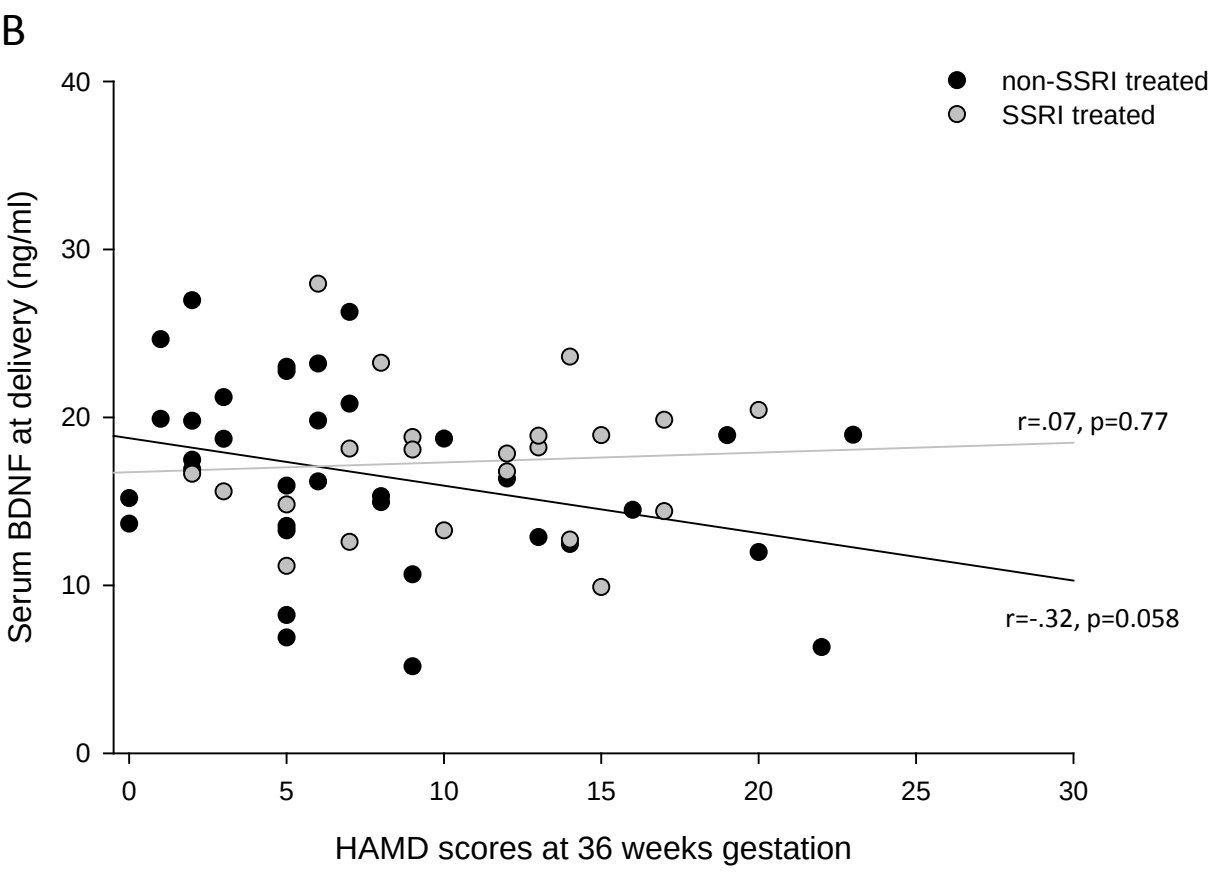
187

Figure 1

A


*
Serum BDNF at 36 weeks gestation (ng/ml)
20
15
10
5
0
Non-SSRI treated
SSRI treated

B


non-SSRI treated
SSRI treated
Serum BDNF at delivery (ng/ml)
40
30
20
10
0
r=.07, p=0.77
r=-.32, p=0.058
0
5
10
15
20
25
30
HAMD scores at 36 weeks gestation

C

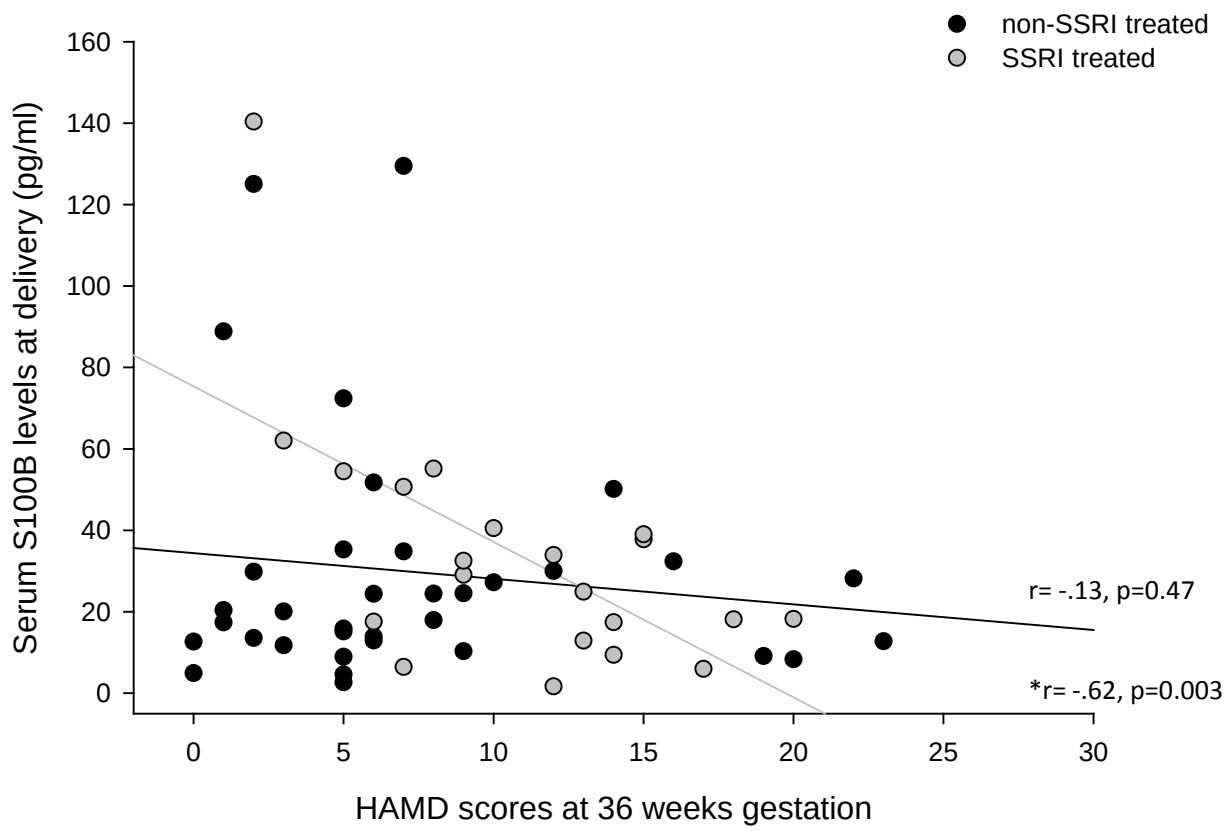

non-SSRI treated
SSRI treated
Serum S100B levels at delivery (pg/ml)
160
140
120
100
80
60
40
20
0
0
5
10
15
20
25
30
HAMD scores at 36 weeks gestation
r= -.13, p=0.47
*r= -.62, p=0.003

Table 1. Mean (±SEM) history of depression or anxiety (% per groups), scores on the HAMD, HAMA, and EPDS, and serum levels of BDNF (ng/ml) and S100B (pg/ml). * denotes significantly different from non-SSRI treated, $p<0.05$.

	Non-SSRI treated	SSRI treated
Depression history (self-report)	13%	90%*
Anxiety history (self-report)	24%	62%*
HAMD at 36 weeks gestation	7.42±.98	10.80±.97*
HAMA at 36 weeks gestation	9.52±1.1	11.84±1.0
EPDS at 36 weeks gestation	4.90±.74	6.31±.85
BDNF at delivery (ng/ml)	16.61±0.92	17.17±0.89
S100B at delivery (pg/ml)	29.90±5.38	34.66±7.18

Ethical approval: "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

References

aan het Rot M, Mathew SJ, Charney DS, (2009) Neurobiological mechanisms in major depressive disorder, CMAJ 180, 305-313.

Bellissima V, Visser GH, Ververs TF, Bel F, Termote JU, Heide M, Gazzolo D, (2015) Antenatal Maternal Antidepressants Drugs Affect S100B Concentrations in Fetal-Maternal Biological Fluids, CNS & neurological disorders drug targets 14, 49-54.

Ben Abdesselam O, Vally J, Adem C, Foglietti MJ, Beaudeux JL, (2003) Reference values for serum S-100B protein depend on the race of individuals, Clin Chem 49, 836-837.

Castren E, Voikar V, Rantamaki T, (2007) Role of neurotrophic factors in depression, Curr Opin Pharmacol 7, 18-21.

Christian LM, Mitchell AM, Gillespie SL, Palettas M, (2016) Serum brain-derived neurotrophic factor (BDNF) across pregnancy and postpartum: Associations with race, depressive symptoms, and low birth weight, Psychoneuroendocrinology 74, 69-76.

Duman RS, Monteggia LM, (2006) A neurotrophic model for stress-related mood disorders, Biol.Psychiatry 59, 1116-1127.

Gao X, Wang J, Yao H, Cai Y, Cheng R, (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.

Guintivano J, Sullivan PF, Stuebe AM, Penders T, Thorp J, Rubinow DR, Meltzer-Brody S, (2017) Adverse life events, psychiatric history, and biological predictors of postpartum depression in an ethnically diverse sample of postpartum women, Psychol Med, 1-14.

Gupta K, Gupta R, Bhatia MS, Tripathi AK, Gupta LK, (2017) Effect of Agomelatine and Fluoxetine on HAM-D Score, Serum Brain-Derived Neurotrophic Factor, and Tumor Necrosis Factor-alpha Level in Patients With Major Depressive Disorder With Severe Depression, J Clin Pharmacol.

Lommatzsch M, Hornych K, Zingler C, Schuff-Werner P, Hoppner J, Virchow JC, (2006) Maternal serum concentrations of BDNF and depression in the perinatal period, Psychoneuroendocrinology 31, 388-394.

Lommatzsch M, Zingler D, Schuhbaeck K, Schloetcke K, Zingler C, Schuff-Werner P, Virchow JC, (2005) The impact of age, weight and gender on BDNF levels in human platelets and plasma, Neurobiol Aging 26, 115-123.

235 Oberlander TF, Warburton W, Misri S, Aghajanian J, Hertzman C, (2006) Neonatal outcomes after
236 prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression
237 using population-based linked health data, Arch Gen Psychiatry 63, 898-906.

238
239 Pawluski JL, Brain UM, Underhill CM, Hammond GL, Oberlander TF, (2012) Prenatal SSRI exposure alters
240 neonatal corticosteroid binding globulin, infant cortisol levels, and emerging HPA function,
241 Psychoneuroendocrinology 37, 1019-1028.

242
243 Pawluski JL, Galea LA, Brain U, Papsdorf M, Oberlander TF, (2009) Neonatal S100B protein levels after
244 prenatal exposure to selective serotonin reuptake inhibitors, Pediatrics 124, e662-670.

245
246 Pawluski JL, Lonstein JS, Fleming AS, (2017) The Neurobiology of Postpartum Anxiety and Depression,
247 Trends Neurosci 40, 106-120.

248
249 Rowe HJ, Fisher JR, Loh WM, (2008) The Edinburgh Postnatal Depression Scale detects but does not
250 distinguish anxiety disorders from depression in mothers of infants, Arch Womens Ment Health 11, 103-
251 108.

252
253 Stroth N, Svenningsson P, (2015) S100B interacts with the serotonin 5-HT7 receptor to regulate a
254 depressive-like behavior, Eur Neuropsychopharmacol 25, 2372-2380.

255
256 Tuohy A, McVey C, (2008) Subscales measuring symptoms of non-specific depression, anhedonia, and
257 anxiety in the Edinburgh Postnatal Depression Scale, Br J Clin Psychol 47, 153-169.

258
259 Vanmierlo T, De Vry J, Nelissen E, Sierksma A, Roumans N, Steinbusch HWM, Wennogle LP, van den
260 Hove D, Prickaerts J, (2018) Gestational stress in mouse dams negatively affects gestation and
261 postpartum hippocampal BDNF and P11 protein levels, Mol Cell Neurosci 88, 292-299.

262
263 Whitaker-Azmitia PM, Murphy R, Azmitia EC, (1990) Stimulation of astroglial 5-HT1A receptors releases
264 the serotonergic growth factor, protein S-100, and alters astroglial morphology, Brain Res. 528, 155-158.

265

266