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1 **Selective Serotonin Reuptake Inhibitor Effects on Neural Biomarkers of Perinatal**
2 **Depression**

3

4 **(Short Communication)**

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25 **Summary**

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

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

32

33

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

35

36 Introduction

37 Our understanding and use of biomarkers that reflect the pathophysiology of maternal
38 depression remains limited. Serum brain-derived neurotrophic factor (BDNF) has been proposed
39 as a biomarker for perinatal depression (Christian et al. 2016; Gao et al. 2016)(Guintivano et al.
40 2017). BDNF is a neurotrophin involved in neuroplasticity and implicated in the
41 pathophysiology and treatment of mood disorders (Castren et al. 2007): with lower serum BDNF
42 levels being associated with depression (aan het Rot et al. 2009). Similarly, during the perinatal
43 period, low serum BDNF levels are associated with increased 3rd trimester depressive symptoms
44 (Christian et al. 2016) and serum BDNF levels are significantly lower in women with postpartum
45 depression (Gao et al. 2016; Lommatzsch et al. 2006). Recent research in rodent models has also
46 shown that gestational stress can reduce levels of BDNF in the hippocampus of the mother
47 (Vanmierlo et al. 2018).

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

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

63 Materials and Methods

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

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

73 None of the mothers took other serotonergic medications during their pregnancies. In the
74 SSRI-treated group, 4 women also took another antidepressant medication and 5 women were
75 also prescribed an antipsychotic. Women in the treated group were on SSRIs for an average of
76 261.07 ± 44.19 (range 94-290) days and, except for 2 women, all women in the SSRI -treated
77 group were on medication for at least 247 days of gestation and all continued SSRI medication
78 up to the time of delivery. Outcomes were compared with mothers not using any medication.
79 Mode of delivery was recorded (vaginal versus C-section). Neonatal outcomes were tabulated
80 from the immediate newborn period. Apgar scores at 1 and 5 minutes, sex, birth weight, head
81 circumference, body length and gestational age were obtained. Only Apgar scores at 1 minutes
82 and gestational age were different between SSRI-exposed and non-exposed neonates where
83 lower Apgar scores at 1 minute and slightly younger gestational ages were evident (Pawluski et
84 al 2012). Demographic information and neonatal characteristics from this cohort of mothers has
85 been published and details can be found there (Pawluski et al. 2012).

86
87 **Maternal Mood.** During pregnancy, maternal anxiety and depression were assessed at the time
88 of study enrollment (approximately 26–28 weeks) and again at 36 weeks gestation (36.2 ± 0.7
89 weeks). *The Hamilton Rating Scale for Depression (HAM-D)*, *The Hamilton Rating Scale for*
90 *Anxiety (HAM-A)*, and *the Edinburgh Postnatal Depression Scale (EPDS)* were used. Self-
91 reported history of depression or anxiety was also asked of each participant at the first visit.

92
93 **Serum BDNF and S100B analysis.** Blood samples were collected at 36 weeks gestation, serum
94 samples were taken at 8 am, 2.5 hours before SSRI medication was taken. Delivery blood
95 samples were taken at term and up to 2 hours after delivery of the placenta from the ante cubital
96 fossa (arm). 33-38 samples of non-SSRI treated women and 22-25 samples of SSRI-treated

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

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

105

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

121

122 **Results**

123 The HAMD, HAMA, and EPDS scores were significantly positively correlated (r 's=.55-
124 .85, p 's=0.00), thus to avoid redundancy HAMD scores were used throughout as our focus was
125 on mood symptoms (HAMA assesses anxiety and the EPDS assesses both depression and
126 anxiety (Rowe et al. 2008; Tuohy and McVey 2008)). The SSRI treated women at 36 weeks
127 gestation had significantly higher HAMD scores compared to non-SSRI treated women ($F(1,$

128 61)=5.43, $p=.02$, Table 1). SSRI-treated women were significantly more likely than non-SSRI
129 treated women to self-report a history of depression ($\chi^2=46.33$, $p=0.00001$) and anxiety
130 ($\chi^2=11.64$, $p=0.0006$; Table 1). Eighty-three percent of the participants identified as being
131 white and there were no significant differences between groups in ethnic diversity ($p=0.5$). SSRI-
132 treated women had a significantly higher BMI at 36wks gestation ($F(1, 82)=6.3602$, $p=.01$,
133 27.4 ± 3.7 for non-treated and 29.9 ± 5.4 for SSRI-treated).

134 Women prescribed SSRIs had significantly higher serum levels of BDNF at 36 weeks
135 gestation ($F(1, 59)=5.7386$, $p=.02$, controlling for BMI and ethnicity, Figure 1A). Furthermore,
136 lower BDNF levels at delivery were marginally associated with increased maternal depressed
137 symptoms during late gestation (36weeks) in non-SSRI treated women (Pearson correlation: $r=-$
138 $.32$, $p=0.058$) but not SSRI treated (Pearson correlation: $r=.07$, $p=.77$, Figure 1B).

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

144 Discussion

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

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

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

165 When looking at serum S100B levels we found that SSRI-treated women have a
166 significant negative correlation between serum S100B levels and maternal mood scores.
167 Serotonin can increase S100B levels (Whitaker-Azmitia et al. 1990) and S100B is known to
168 alleviate depressive-like symptoms via its actions on the 5-HT7 receptor (Stroth and
169 Svenningsson 2015), thus it may be that the increase in serotonin activity at the synaptic cleft,
170 after SSRI treatment, increases S100B and decreases symptoms of depression via actions on the
171 5-HT7 receptor.

172 **Conclusion**

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

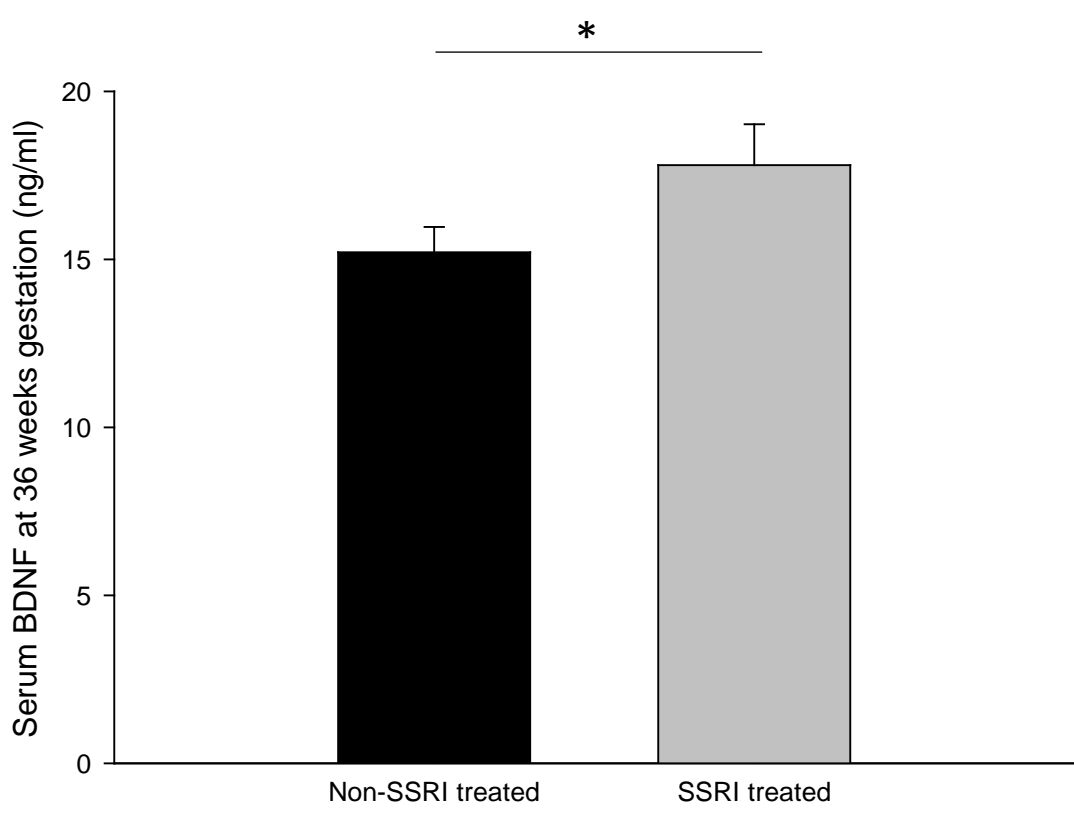
178 **Figure legend**

179

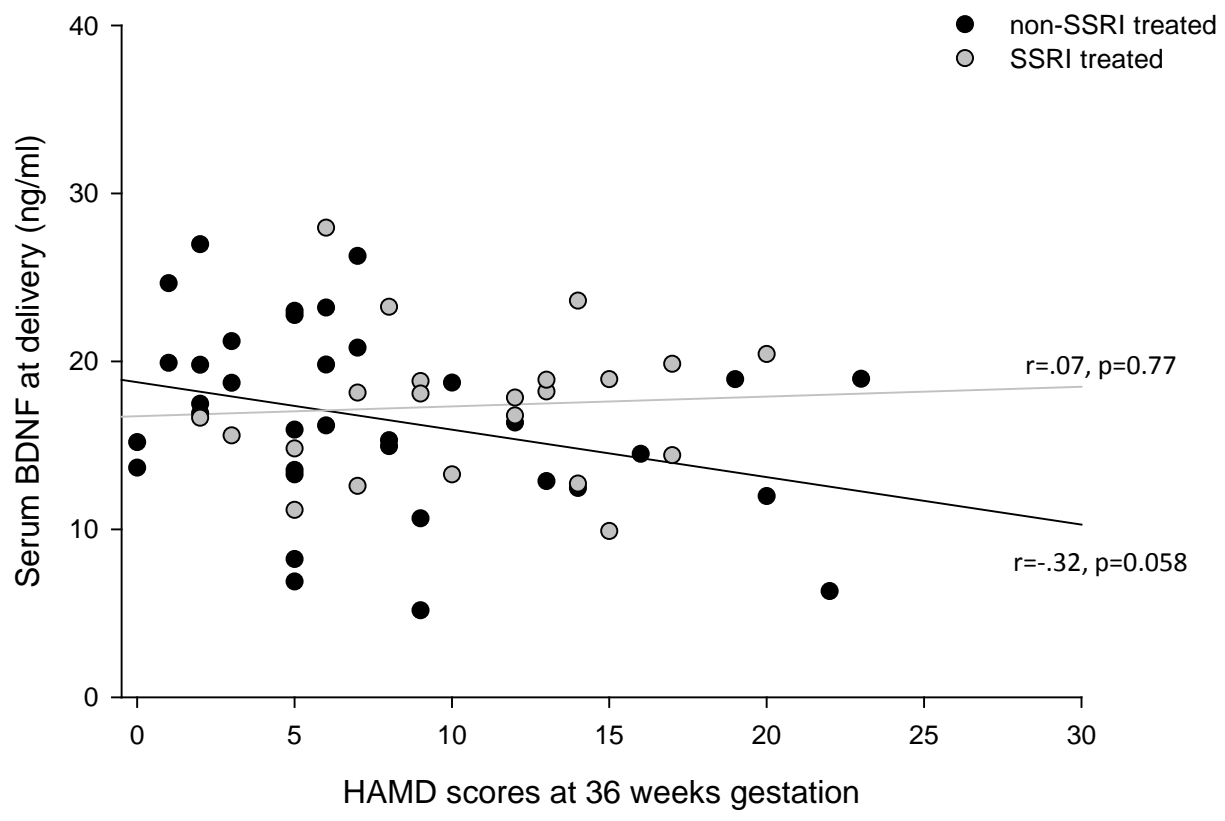
180 **Figure 1.** Serum biomarkers (S100B and BDNF) and maternal depression symptoms in SSRI
181 treated and non-SSRI treated women. A) Mean (\pm SEM) serum BDNF levels at 36 weeks
182 gestation ($F(1, 59)=5.7, p=.02$). B) Correlations between serum BDNF levels at delivery and
183 maternal depression 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 $p<0.05$.

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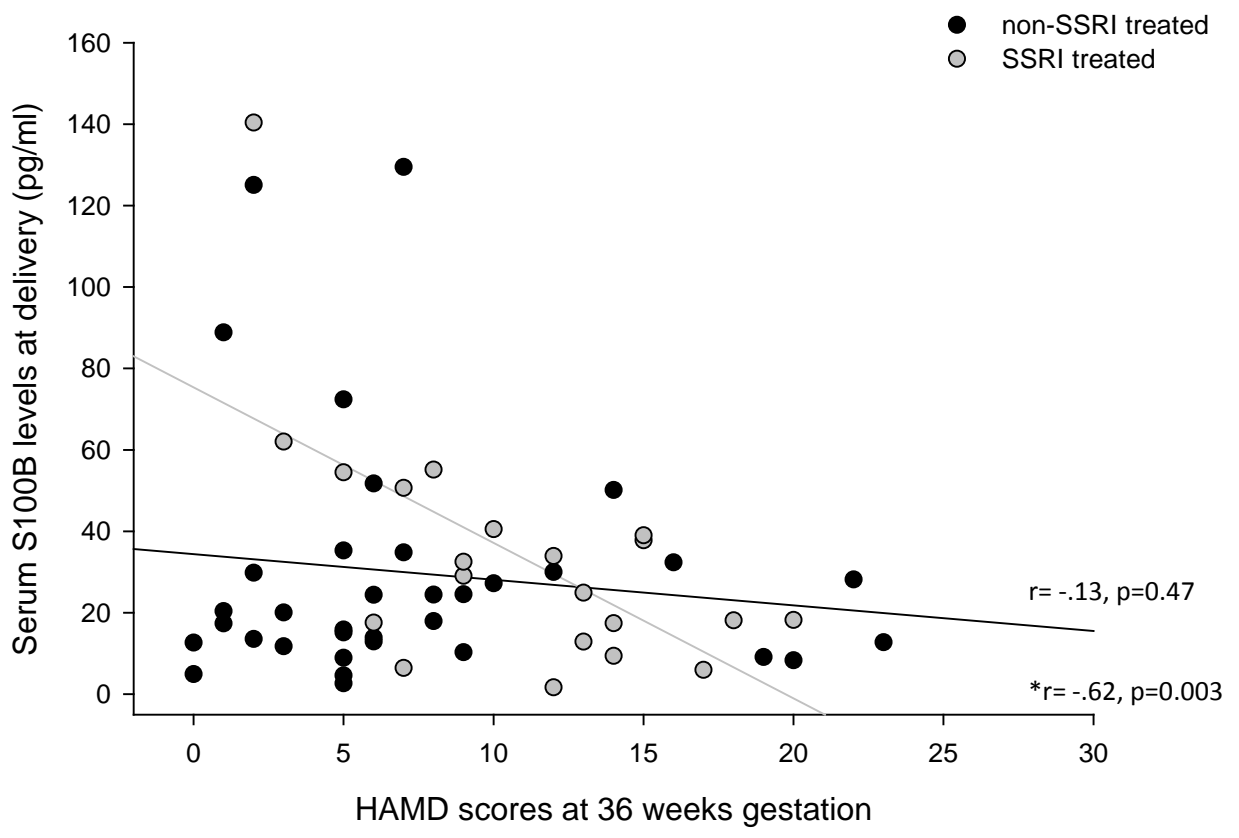
Figure 1
A



B



C



188 **Table 1.** Mean (\pm SEM) history of depression or anxiety (% per groups), scores on the HAMD, HAMA,
 189 and EPDS, and serum levels of BDNF (ng/ml) and S100B (pg/ml). * denotes significantly different from
 190 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 \pm .98	10.80 \pm .97*
HAMA at 36 weeks gestation	9.52 \pm 1.1	11.84 \pm 1.0
EPDS at 36 weeks gestation	4.90 \pm .74	6.31 \pm .85
BDNF at delivery (ng/ml)	16.61 \pm 0.92	17.17 \pm 0.89
S100B at delivery (pg/ml)	29.90 \pm 5.38	34.66 \pm 7.18

191

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

195

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