The role of steroids in the development of post-partum mental disorders

Andrea Paskova^a, Roman Jirak^c, Michaela Mikesova^a, Karolina Adamcova^a, Zdenka Fartakova^a, Vladimira Horakova^a,
Michal Koucky^a, Martin Hill^{a,b}, Hana Hruskovicova^b, Luboslav Starka^b, Michaela Duskova^b, Antonin Parizek^a

Background. Unfavorable post-partum changes to mental well-being affect more than half of all women, and are a risk to the health of both mother and baby. Their effects place strains on health and social systems. Currently, no generally accepted theory exists of the causes and mechanisms of post-partum mental disorders.

Methods. Literature search up to 2012, using PubMed and search words: neuroactive steroids, post-partum mental disorders, depression, corticotropin-releasing hormone and estrogens.

Results. There are several theories for post-partum depression. One is that autoimmune diseases are involved. Others revolve around genes responsible or that lead to increased disposition to the disorder. It is likely however that the process is associated with the separation of the placenta and the fetal zone of fetal adrenal gland, the main sources of corticotropin-releasing hormone and sexual and neuroactive steroids during pregnancy, and the ability of the receptor system to adapt to these changes. The central nervous system is able to produce neurosteroids, but the drop in levels of peripheral steroids likely leads to a sudden deficit in neuroinhibitory steroids modulating ionotropic receptors in the brain.

Conclusions. Post-partum depression is a multifactorial disease with unknown etiology. It is probably associated with sudden changes in the production of hormones influencing the nervous system, and on the other hand the ability of the receptor system to adapt to these changes. When the relative changes in concentrations of hormones, rather than their absolute levels, is likely more important.

Key words: neuroactive steroids, postpartum depression, corticotropin-releasing hormone, estrogens, allopregnanolone

Received: April 15, 2012; Accepted: October 18, 2012, Available online: November 12, 2012
<http://dx.doi.org/10.5507/bp.2012.098>

^aDepartment of Obstetrics and Gynecology, 1st Faculty of Medicine and General Teaching Hospital in Prague, Czech Republic

^bInstitute of Endocrinology, Prague

^cDepartment of Psychiatry, 1st Faculty of Medicine, Charles University in Prague and General University Hospital in Prague

Corresponding author: Antonin Parizek, e-mail: parizek@porodnice.cz

INTRODUCTION

Steroid hormones act through two different pathways. The classic effect is at the genomic level, acting over slow time scales of hours to days. The non-genomic effect of steroids on the other hand can influence cellular processes in seconds or even milliseconds. Steroid hormones that act in this non-genomic way and influence neural excitability are known as neuroactive steroids. Those that are produced in the brain are called neurosteroids. The molecular mechanisms for these direct effects, influencing neural stimulation through the modulating function of various ligands activating ion channels, were already described in the 1980s and 90s. These steroids also act as transcription factors. For this reason their activity has been studied in psychological and neurological disorders, mostly in depressive and anxiety disorders, reactions to stress, premenstrual tension, epilepsy, alcoholism, and in cognitive function disorders including Alzheimer's disease.

NEUROACTIVE STEROIDS AND DEPRESSION

It has been demonstrated that neurosteroids play a large role in the onset, course, and treatment of depression. In animal models, it has been shown that administering the antidepressant fluoxetine, a member of the class of selective serotonin reuptake inhibitors (SSRI), markedly increases allopregnanolone levels in the brain¹. In contrast, in animals with induced depressive symptoms directly given allopregnanolone, the symptoms of depression lessened². Severe depression in people is associated with lowered brain levels of allopregnanolone and simultaneously increased levels of tetrahydrodeoxycorticosterone (THDOC), and treatment with fluoxetine increases the levels of allopregnanolone³. SSRI-type antidepressants likely increase the levels of allopregnanolone through the activation of enzymes involved in the synthesis of 3- α -reducing neurosteroids⁴.

It is also surmised that the additional neurosteroids: dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and pregnenolone sulfate (PS) have antidepressant effects in humans and in animal models. Clinical studies have not been unequivocal however,

and DHEA is not recommended for treating depression or for augmenting antidepressant therapy according to evidence-based medicine. Even the brain concentration levels of DHEA in depressive patients are equivocal.

A very important discovery was that neurosteroids may change the excitability of neuronal interactions with specific neurotransmitter receptors. Most attention has been given to the receptor for gamma-aminobutyric acid receptor (GABA) type GABA_A, an ionotropic receptor associated with a chloride ion channel. After ligand binding, GABA leads to hyperexcitation of the neuronal membrane, preventing further stimulation. GABA_A receptors are inhibitory, but the GABA system is not always inhibitory. In the fetus, it is stimulatory. These receptors are created from various subunits (alpha, beta, gamma, and others). The chloride channel is made of a combination of five subunits. The binding site for GABA is between subunits alpha and beta. The GABA_A receptor is allosterically influenced by various types of substances. Benzodiazepines interact with the combination of subunits (alpha1)2 (beta2)2 gamma2, and with other combinations^{5,6}. In addition to benzodiazepine, the Z hypnotics (zolpidem, zopislon, zaleplon, etc) also bind to this site. Other allosteric sites, working at the level of the chloride channel, are the barbiturate site, where barbiturates bind, the site for general anesthesia, where for instance propofol, steroids, halotan and ethylalcohol bind, and the so called picrotoxin site, where for instance the agonist clomethiazol binds.

Some neurosteroids act as substances modulating the GABA_A receptors, binding to these receptors allosterically. Dehydroepiandrosterone (DHEA), which is synthesized in brain astrocytes and elsewhere, has an antagonistic effect on GABA_A. It improves memory, lengthens REM sleep (during which long-term memories are stored). Decreased levels of DHEA are generally found in depressed patients, and its administration improves the symptoms of depression and cognitive function^{7,8}. Similar effects have been found for dehydroepiandrosterone sulfate (DHEAS).

Severe depression in humans is characterized by an imbalance in endogen neurosteroids. The levels of allopregnanolone and some other alpha-reduced neurosteroids are reduced in the brain fluid as well as the plasma. Allopregnenolone is an allosteric modulator of the GABA_A receptor. It has been shown that modulation of the GABA_A receptor has great importance for the onset of depression and for its treatment. Some synthetic neurosteroids will likely be used as new antidepressants⁹.

POST-PARTUM MENTAL DISORDERS

Post-partum mental disorders (PPMD) occur in some form in more than half of women. In most cases these are temporary, without long-term negative consequences. However, there remain a relatively significant proportion of women for whom the complications lead to aftereffects for themselves and even for their children. Some of these

negative effects can appear with a significant delay, even in puberty or adulthood. In the most serious cases, mental disorders associated with the end of pregnancy can lead to tragic consequences, including suicide of the mother or infanticide. In any case, post-partum mental disorders are a significant risk to the health of the mother and child, and dealing with these disorders has long been a strain on health and social systems.

PPMD can be divided into three categories: Post-partum blues (PPB) occurs in 50-70% of mothers and usually disappears by itself within a week without the need for specific therapy. Mothers suffering from PPB experience a temporary phase of emotional weakness around the second to fifth day after birth. This temporary psychopathological PPB is similar to premenstrual tension, with irritability being the main symptom. In fact PPB is not depression, but a sudden and unexpected fluctuation in mood including anxiety, discouragement, perplexity, lack of concentration, and forgetfulness. The etiology of PPB has not yet been elucidated, though many hypotheses have been proposed¹⁰.

Post-partum depression (PPD), occurring in 10-15% of births, is a significant depressive state occurring most frequently between the fourth and sixth week of pregnancy¹¹. It is estimated that almost half of these cases go undocumented. PPD manifests as symptoms of depressive moods, sleep disorders, anxiety, loss of interest and psychological imbalance, feelings of guilt, even suicidal thoughts¹². Post-partum psychosis (PPP) (occurrence of about 0.1-0.2%) is most often the result of bipolar and schizophrenic disorders. They require hospitalization due to the risk of suicide or infanticide¹².

CORTICOTROPIN-RELEASING HORMONE AND POST-PARTUM DEPRESSION

Despite the existence of some hypotheses, there is no current generally accepted theory of the causes and mechanisms of post-partum mental disorders¹³⁻¹⁵. The separation of the placenta and the fetal compartment of the fetal adrenal gland likely plays an important role in the mechanism of PPMD, since they are the main sources of corticotropin-releasing hormone (CRH) and steroids during pregnancy. CRH has been identified in various organs and systems including the immune system and reproductive systems of both sexes. CRH immunoreactivity has been documented in peripheral sites of inflammation, the ovaries, endometrium, placenta, deciduum, and testes. In addition, CRH plays a direct immunomodulatory role as an autocrine/paracrine mediator of inflammation, and regulates reproductive functions including inflammatory components, such as ovulation, luteolysis, decidualization, and implantation. Placental CRG thus influences the physiology of pregnancy and the onset of birth¹⁶.

CRH is primarily a regulator of the hypothalamo-hypophyseal-adrenal axis (HPA), which is closely associated with stress. The activity of HPA is markedly increased in patients with depression. Various related hypothalamic

peptidergic systems have close connections to the symptoms of depression. Increased production of vasopressin, which further stimulates the release of ACTH induced CRH in depression and which has been colocalized in neurons producing CRH and neuronal nucleus supraopticus (SON), are associated with suicide risk. The increased activity of oxytocin producing neurons in the paraventricular nucleus (PVN) can be related with disorders in food intake. On the other hand, the suprachiasmatic nucleus (SCN), which functions as a biological clock of the brain, shows lowered production of vasopressin in depression, which could explain sleep problems in depressed patients as well as play a role in the marked activation of CRH (ref.¹⁷).

STEROIDS AND POST-PARTUM DEPRESSION

When the placenta is discharged during birth, the source of almost all pregnancy CRH and placental steroids, i.e. estrogen, progesterone, and its neuroactive reduced metabolites, is also removed. In addition, the source of precursors to placental steroids, the fetal zone of the fetal adrenal gland, is also removed. The most abundant pregnancy 3β -hydroxy-5-en steroids produced here, i.e. pregnenolone sulfate and dehydroepiandrosterone sulfate, are also neuroactive steroids. Long-term extreme increased levels of neuroinhibitory pregnane steroids in the periphery evidently lead to their more intense penetration across the hematoencephalic barrier to the central nervous system (CNS), where they induce negative compensation mechanisms, consisting of lowered affinity of the $GABA_A$ receptor for neuroinhibitory pregnane steroids. The CNS is able to produce a certain amount of its own neuroactive steroids¹⁸, but despite this, a decrease in the levels of peripheral steroids could produce a sudden deficit of neuroinhibitory steroids acting mainly through the modulation of $GABA_A$ -r. The question remains how quickly can ionotropic receptors in the brain adapt to the significantly lowered influx of steroid modulators from the periphery, and whether possible defects in this synchronization may be related to manifestation of PPMD, as some studies have indicated¹⁹. Other studies have found increased prenatal levels of progesterone in women with PPD compared to controls, and a quicker decrease in these levels to levels comparable²⁰ or even lower²¹ than controls.

Neuroinhibitory pregnane steroids may also mediate the inhibition of 5-hydroxy-tryptamine neurons through modulation of the $GABA_A$ -r, which could be significant for the relationships of changes in mood to changes in reproductive hormones, such as in PPD (ref.²²). They are also increased along with the amount of dopamine released in the nucleus accumbens, and thus likely influence mood and motivation²³.

There currently exists only one study on the relationship between pregnane steroids and PPMD. Allopregnanolone, progesterone, cortisol, prolactin and estradiol were measured in 40 healthy primiparas after the

birth of healthy children. On the same day, each volunteer answered the "Hamilton Rating Scale for Depression" questionnaire for psychometric evaluation and the "Stein Questionnaire" for symptoms of PPB (ref.²⁴). 18 women (45%) were evaluated as being PPB positive. These women had lowered levels of allopregnanolone, though the corresponding differences in progesterone levels were not statistically significant. The levels of progesterone were correlated in PPB-negative women, though not in PPB-positive. There was a significant negative correlation found between Hamilton score and levels of allopregnanolone and progesterone²⁴.

In addition to progesterone and its neuroactive metabolites, estrogen can also be associated with the etiology of PPMD. Estrogens influence the mental state of memory through classical monoamine and neurotransmitter receptor mechanisms in the brain, and low levels of estrogens are associated with PPD. Furthermore, estrogens stimulate an increase in dopamine receptors, and increase the density of 5-hydroxy-tryptamine binding sites in brain regions controlling mood, mental status, cognitive functions, emotions and behavior.

In rodents, estrogens also stimulate the expression of the arginine-vasopressin gene in the stria terminalis, a region storing social and olfactory memories. Described mechanisms indicate the protective role of estrogens²⁵, which has been supported by their success in the treatment of women with PPD (ref.^{26,27}), as well as the negative effects observed when estrogen applications were interrupted in studies of women²⁸.

Results from one study show a drop in the activity of brain cortical sulfatase and growth in the concentration of DHEAS in this brain region after suddenly ending estradiol in rats, which could lead to depressed activity in $GABA_A$ -r. The authors speculate on the relevance of this phenomenon to PPMD (ref.²⁹).

The role of estrogen in the development of post-partum depression has led to considerations of its use in treatments. Ahokas et al. tried giving estrogen substitution to women with PPD who were hypogonadal. After one week, depressive symptoms were reduced by half³⁰. Gregoire et al. undertook a placebo-controlled study, in which women with PPD were given transdermal 17β -estradiol (200 ug daily) and cyclic dydrogesterone (10 mg per day, 12 days per month), or a placebo. After a month of treatment the women taking estrogens had a four-fold reduction in depressive symptoms compared to those taking the placebo³¹. Due to a lack of experience, however, estrogen substitution is considered a complimentary method to conventional treatments with anti-depressives. The results of studies so far indicate that the response to estrogen substitution is rapid, with minimal side-effects, and minimal transfer to mother's milk, giving hope for the role of estrogens in the treatment of PPD (ref.³²).

CONCLUSIONS

The etiology of post-partum depression is as yet unknown. It is clear that it is a multifactorial disease, with various internal and external factors playing a role. Despite several hypotheses, there is no generally accepted theory on the causes and mechanisms of post-partum mental disorders. It is probable however, that the process is associated with sudden changes in the production of hormones influencing the nervous system, and on the other hand the ability of the receptor system to adapt to these changes. The relative concentrations of hormones, rather than their absolute levels, is likely most important.

ACKNOWLEDGEMENTS

This work has been supported by grant IGA MZ CR no NS 9790-4, NT 12211-5 and NT 13890, by the project MZ CR for conceptual development of research organization 00023761 (Institute of Endocrinology, Prague, Czech Republic) and SVV UK 2012 no 264501.

Authorship contributions: APas: literature search and manuscript writing; MM, KA, ZF, VH, MK: literature search of the area obstetrics; HH MD, MH: literature search of the area steroids and manuscript writing; RJ, LS, APAr: final approval.

Conflict of interest statement: The authors stated that there are no conflicts of interest regarding the publication of this article.

REFERENCES

- Uzunov DP, Cooper TB, Costa E, Guidotti A. Fluoxetine – elicited changes in brain neuroactive steroid content measured by negative ion mass fragmentography. *Proc Natl Acad Sci U S A* 1996;93:12599-604.
- Khisti RT, Chopde CT. Serotonergic agents modulate antidepressant-like effect of the neuroactive steroid 3 α -hydroxy-5 α -pregnan-20-one in mice. *Brain Research* 2000;868:291-300.
- Strohle A, Pasini A, Romeo E, Hermann B, Spalletta G, di Michele F, Holsboer F, Rupprecht R. Fluoxetine decreases concentrations of 3 α ,5 α -tetrahydrodeoxycorticosterone (THDOC) in major depression. *Journal of Psychiatric Research* 2000;34:183-6.
- Mellon SH, Griffin LD, Compagnone NA. Biosynthesis and action of neuroactive steroids. *Brain Research Reviews* 2001;37:3-12.
- Froestl W. Chemistry and pharmacology of GABA_B receptor ligands. *Adv Pharmacol* 2010;58:19-62.
- Baur R, Kaur KH and Sigel E. Structure of α 6 β 3 δ GABA_A receptors and their lack of ethanol sensitivity. *Journal of Neurochemistry* 2009;111:1172-81.
- Baulieu EE, Thomas G, Legrain S, Lahlou N, Roger M, Debuire B, Fauconau V, Girard L, Hervy MP, Latour F, Leaud MC, Mokrane A, Pitti-Ferrandi H, Trivale C, de Lacharrière O, Nouveau S, Rakoto-Arison B, Souberbielle JC, Raison J, Le Bouc Y, Raynaud A, Girerd X, and Forette F. Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: Contribution of the DHEAge Study to a sociobiomedical issue. *PNAS* 2000;97:4279-84.
- Reddy DS. Neurosteroids: Endogenous role in the human brain and the therapeutic potentials. *Prog Brain Res* 2010;186:113-37.
- Schüle C, Eser D, Baghai TC, Nothdurfter C, Kessler JS, Rupprecht P. Neuroactive steroids in affective disorders: target for novel antidepressant or anxiolytic drugs? *Neuroscience* 2011;191:55-77.
- Lanczik M, Brockington IF. Postpartum dysphoric syndrome. *Psychopathology, diagnosis and etiology. Fortschr Neurol Psychiatr* 1999;67:60-7.
- Godfroid IO, Charlot A. Postpartum psychiatry. *Rev Med Brux* 1996;17:22-3.
- Kemp B, Bongartz K, Rath W. Psychic disturbances in the postpartum period: an increasing problem? *Z Geburtshilfe Neonatol* 2003;207:159-65.
- Gleicher N. Postpartum depression, an autoimmune disease? *Autoimmun Rev* 2007;6:572-6.
- Mitchell C, Notterman D, Brooks-Gunn J, Hobcraft J, Garfinkel I, Jaeger K, Kotenko I, McLanahan S. Role of mother's genes and environment in postpartum depression. *Proc Natl Acad Sci USA* 2011;17:8189-93.
- Maguire J, Mody I. GABA_A plasticity during pregnancy: relevance to postpartum depression. *Neuron* 2008;59:207-13.
- Kalantaridou S, Makriganakis A, Zoumakis E, Chrousos GP. Peripheral corticotropin-releasing hormone is produced in the immune and reproductive systems: actions, potential roles and clinical implications. *Front Biosci* 2007;12:572-80.
- Swaab DF, Bao AM, Lucassen PJ. The stress system in the human brain in depression and neurodegeneration. *Ageing Res Rev* 2005;4:141-94.
- Stoffel-Wagner B. Neurosteroid biosynthesis in the human brain and its clinical implications. *Ann NY Acad Sci* 2003;1007:64-78.
- Beckley EH, Finn DA. Inhibition of progesterone metabolism mimics the effect of progesterone withdrawal on forced swim test immobility. *Pharmacol Biochem Behav* 2007;87:412-9.
- Chang J, Zhang Y, Cui L. Impact of placental hormone withdrawal on postpartum depression. *Zhonghua Fu Chan Ke Za Zhi* 1995;30:342-4.
- Harris B, Lovett L, Newcombe RG, Read GF, Walker R, Riad-Fahmy D. Maternity blues and major endocrine changes: Cardiff puerperal mood and hormone study II. *BMJ* 1994;308:949-53.
- Kaura V, Ingram CD, Gartside SE, Zouny AH, Judge SJ. The progesterone metabolite allopregnanolone potentiates GABA(A) receptor-mediated inhibition of 5-HT neuronal activity. *Eur Neuropsychopharmacol* 2007;17:108-15.
- Rouge-Pont F, Mayo W, Marinelli M, Gingras M, Le Moal M, Piazza PV. The neurosteroid allopregnanolone increases dopamine release and dopaminergic response to morphine in the rat nucleus accumbens. *Eur J Neurosci* 2002;16:169-73.
- Nappi RE, Petraglia F, Luisi S, Polatti F, Farina C, Genazzani AR. Serum allopregnanolone in women with postpartum "blues". *Obstet Gynecol* 2001;97:77-80.
- Fink G, Sumner BE, Rosie R, Grace O, Quinn JP. Estrogen control of central neurotransmission: effect on mood, mental state, and memory. *Cell Mol Neurobiol* 1996;16:325-44.
- Ahokas A, Kaukoranta J, Aito M. Effect of oestradiol on postpartum depression. *Psychopharmacology (Berl)* 1999;146:108-10.
- Gregoire AJ, Kumar R, Everitt B, Henderson AF, Studd JW. Transdermal estrogen for treatment of severe postnatal depression. *Lancet* 1996;347:930-3.
- Bloch M, Schmidt PJ, Danaceau M, Murény J, Nieman L, Rubinow DR. Effects of gonadal steroids in women with a history of postpartum depression. *Am J Psychiatry* 2000;157:924-30.
- Maayan R, Strous RD, Abou-Kaoud M, Weizman A. The effect of 17 β estradiol withdrawal on the level of brain and peripheral neurosteroids in ovariectomized rats. *Neurosci Lett* 2005;384:156-61.
- Ahokas A, Kaukoranta J, Wahlbeck K, Aito M. Estrogen deficiency in severe postpartum depression: successful treatment with sublingual physiologic 17 β -estradiol: a preliminary study. *J Clin Psychiatry* 2001;62(5):332-6.
- Gregoire AJ, Kumar R, Everitt B, Henderson AF, Studd JW. Transdermal oestrogen for treatment of severe postnatal depression. *Lancet* 1996;347:930-3.
- Moses-Kolko EL, Berga SL, Kalro B, Sit DK, Wisner KL. Transdermal estradiol for postpartum depression: a promising treatment option. *Clin Obstet Gynecol* 2009;52:516-29.