# Steroid Hormones in the Development of Postpartum Depression

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**Summary**

Postpartum depression affects 10-15 % women after childbirth. There is no currently generally accepted theory about the causes and mechanisms of postpartum mental disorders. The principal hypothesis concerns the association with sudden changes in the production of hormones affecting the nervous system of the mother and, on the other hand, with the ability of receptor systems to adapt to these changes. We observed changes in steroidogenesis in the period around spontaneous delivery. We collected three samples of maternal blood. The first sampling was 4 weeks prior to term; the second sampling was after the onset of uterine contractions (the beginning of spontaneous labour); the third sampling was during the third stage of labour (immediately after childbirth). Additionally, we collected mixed umbilical cord blood. The almost complete steroid metabolome was analyzed by gas chromatography-mass spectrometry followed by RIA for some steroids. Mental changes in women in the peripartum period were observed using the Hamilton Depression Rating Scale. The local Ethics Committee approved the study. We found already the changes in androgens levels correlating with postpartum mood disorders four weeks prior to childbirth. The strongest correlations between steroid and postpartum mood change were found in venous blood samples collected from mothers after childbirth and from umbilical cord blood. The main role played testosterone, possibly of maternal origin, and estrogens originating from the fetal compartment. These results suggest that changes in both maternal and fetal steroidogenesis are involved in the development of mental changes in the postpartum period. Descriptions of changes in steroidogenesis in relation to postpartum depression could help clarify the causes of this disease, and changes in some steroid hormones are a promising marker of mental changes in the postpartum period.

**Key words**

Postpartum depression • Neuroactive steroids • Testosterone • Estrogens

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## Introduction

Postpartum changes in mental well-being or even disorders affect more than 50 % of women. For the most part, this is a transient phenomenon without more serious consequences. There are, however, a significant number of women where these complications lead to consequences not only in the women themselves but also in their children (Wiesner *et al.* 2006). Some of these negative changes may occur even after a considerable period of time, e.g. in puberty or even in adulthood. In the most serious cases of mental disorders associated with the termination of pregnancy, tragic events e.g. the mother's suicide or killing of the child may occur. In any case, postpartum mental disorders present a serious health risk to both mother and child, and dealing with the consequences burdens health and social systems often on

a long-term basis.

Postpartum depression (PPD) affecting 10-15 % of women after childbirth is a significantly depressive condition, occurring most frequently between the fourth and sixth weeks of the postpartum period (Godfroid and Charlot 1996). PPD is manifested by symptoms of a depressive mood, sleep disorders, anxiety, loss of interest and mental balance, from feelings of guilt to suicidal thoughts (Kemp *et al.* 2003).

Despite several hypotheses, there is currently no generally accepted theory about the causes and mechanisms of postpartum mental disorders. However, it is likely that this process is associated with sudden changes in the production of nervous system affecting hormones and, on the other hand, with the ability of receptor systems to adapt to these changes.

Removal of the placenta during birth leads to the removal of not only nearly all pregnancy corticotropin-releasing hormone but also placental steroids, i.e. estrogens, progesterone and its neuroactive metabolites. In particular, the source of placental steroid precursors is removed, i.e. the fetal zone of the fetal adrenal gland. The most abundant pregnancy 3β-hydroxy-5-ene steroids, i.e. pregnenolone sulphate and dehydroepiandrosterone sulphate, are also neuroactive steroids.

Although the central nervous system of the mother is able to produce a certain amount of its own neuroactive steroids (Stoffel-Wagner 2003), the decrease in peripheral steroids levels could cause a sudden deficit of neuroinhibitory steroids acting primarily through modulation of $GABA_A$-R (γ-aminobutyric acid A receptor). The question remains how quickly ionotropic receptors in the brain are able to adapt to a significantly reduced supply of steroid modulators from the periphery, and whether any disorders in the synchronization could be related to the manifestation of PPD, as indicated in several studies (Beckley and Finn 2007).

In our study, we focused on changes in steroidogenesis in the periods before, during and after childbirth in relation to the development of mental disorders in the postpartum period.

## Methods

In our study, we randomly selected 44 women from the pool of those women observed prior to childbirth at the Department of Obstetrics and Gynecology of the First Faculty of Medicine and General Teaching Hospital in Prague. Only healthy women with a physiological course of pregnancy with no psychiatric illness in their history, and who did not use any steroidogenesis-affecting drugs were included.

All examinations and collecting of samples were conducted at the Department of Obstetrics and Gynecology of the First Faculty of Medicine and General Teaching Hospital in Prague. The measurement was performed on Institute of Endocrinology. The first examination was performed four weeks prior to term, it was consisted of taking a medical history, filling the standard Hamilton Depression Rating Scale (HAM-D) was filled in and collecting of 10 ml of venous blood. HAM-D confirmed physiological mental condition of women before parturition. The second sampling was performed after the onset of uterine contractions (the beginning of spontaneous labour). The third sampling was performed during the third stage of labour (immediately after childbirth). Additionally, we collected mixed umbilical cord blood.

Postpartum depression levels were determined using the standard HAM-D, three times in total after birth: three weeks after childbirth, six weeks after and six months after.

The group was divided into three sub-groups according to the seriousness of the postpartum depression according to the standard HAM-D. The first group consisted of 25 women with no symptoms of depression. The second group included 10 women with mild depression, and the third group included 9 women with moderate to severe depression. We did not encounter any women with postpartum psychosis. The Hamilton Depression Rating Scale is designed to assess depression levels, especially where this needs to be assessed repeatedly at shorter intervals (e.g. prior, during or upon the completion of treatment). Hamilton Depression Rating Scale is used worldwide and is probably the most commonly used scale in depression assessment. The rating is conducted through interviews with the patient lasting 15 to 20 minutes on average. It consists of 17 basic items related to depression providing a basis for scoring (+ four additional items). Eight items are based on a five-point rating, where zero indicates the symptom is not present and four indicates the symptom is severe (strongly expressed). Nine items have a three-point rating (0-2).

The evaluation of the Hamilton Depression Rating Scale is based on the score from the first 17 items: 0-7 = normal mood; 8-13 = mild depression; 14-18 = moderate depression; 19-22 = severe depression; => 23 =

very severe depression (Hamilton 1960).

The Ethical Committee of the Institute of Endocrinology approved the study, and all patients signed informed consent forms before participating in the study.

All samples were measured using gas chromatography-mass spectrometry on a GCMS-QP2010 Plus (Shimadzu, Japan). The system consisted of a gas chromatograph equipped with automatic flow control, an AOC-20s auto-sampler and a quadrupole electron-impact detector with an adjustable electron voltage of 10-195 V. A capillary column with a medium polarity RESTEK Rxi (diameter 0.25 mm, length 15 m, film thickness 0.1 μm) was used for analyses.

Pregnenolone, progesterone, 5α-dihydro-progesterone, allopregnanolone, isopregnanolone, pregnanolone, 20α-dihydropregnenolone, 20α-dihydro-progesterone, conjugated 5α-pregnane-3β,20α-diol, 16α-hydroxypregnenolone, androstenediol, androstenedione, dehydroepiandrosterone, testosterone, 5α-dihydrotesto-sterone, androsterone, epiandrosterone, etiocholanolone, 7α-hydroxydehydroepiandrosterone, 7β-hydroxydehydro-epiandrosterone, 5-androstene-3β,7α,17β-triol and 5-androstene-3β,7β,17β-triol and polar conjugates, measured using our gas chromatography-mass spectrometry method (GC-MS) published in detail elsewhere (Hill *et al.* 2010a). Luteinizing hormone and follicle stimulating hormone were estimated using immunoradiometric assay (IRMA) kits from Immunotech (France). Sex hormone binding globulin was assayed by IRMA kit (Orion, Espoo Finland). Cortisol was measured by a radioimmunoassay (RIA) kit from Orion (Finland). 17-Hydroxyprogesterone was measured using a RIA kit from Immunotech (France). The immunoassays were processed on a Stratec (France) automatic analyser. Free and conjugated 17-hydroxypregnenolone was measured using our previously published methods (Hill *et al.* 1999, Vcelakova *et al.* 2007).

The data obtained were statistically evaluated using Kruskal-Wallis test robust ANOVA followed by robust Dunn's multiple comparisons with Bonferroni correction.

## Results

We monitored changes in steroid levels in maternal blood during the first three sample collections (i.e. four weeks prior to childbirth, after the onset of uterine contractions (the beginning of labour), and in the 3rd stage of labour (immediately after childbirth) and in mixed umbilical cord blood. Some of the changes in steroid hormone levels found were shown to be significant of the development of depression in the postpartum period.

Four weeks prior to childbirth, we found already the changes in androgens levels correlating with postpartum mood disorders (Table 1). In contrast, steroid hormone levels at the onset of uterine contractions there were no changes related to postpartum mood disorders. Overall, however, the strongest changes were found in samples collected after childbirth. Both testosterone, most likely of maternal origin (Table 2), and estrogens from the fetal compartment (Table 3) played the main role. Testosterone from umbilical cord blood did not change.

**Table 1.** Significant changes in steroid levels related to postpartum mental disorders in maternal blood four weeks prior to the labour.

| Variable | Without depression | Mild depression | Moderate depression |
|---|---|---|---|
| *Age* | 33 (31, 37) | 31.5 (29.5, 32.8) | 33 (31, 34) |
| *Androstenedione* | 5.28 (3.21, 6.94) | 7.22 (5.74, 9.14)* | 8.1 (6.81, 13.8)* |
| *5β-Dihydroprogesterone* | 1.09 (0.91, 1.8) | 0.817 (0.62, 1.08) | 1.29 (0.979, 1.65)* |
| *Androsterone* | 0.383 (0.21, 0.526) | 0.432 (0.363, 0.537) | 0.495 (0.378, 0.954)* |
| *5α-Androstane-3α, 17β-diol* | 0.0352 (0.026, 0.0727) | 0.0345 (0.0191, 0.0688) | 0.112 (0.0772, 0.236)* |
| *17-Hydroxypregnenolone* | 0.68 (0.34, 1.49) | 1.45 (0.845, 2.21)* | 1.13 (0.42, 2.34)* |
| *Testosterone* | 3.69 (2.83, 4.66) | 4.01 (3.46, 5.03) | 4.68 (4.4, 5.76)* |

Significance level (*) $p<0.05$ Kruskal-Wallis test. Groups did not differ in age. Levels are shown as the median and quartiles in (nM).

**Table 2.** Significant changes in steroid levels related to postpartum mental disorders in maternal blood after childbirth.

| Variable | Mild depression | Moderate depression | Without depression |
|---|---|---|---|
| *Age* | 33.5 (30.3, 36.5) | 31 (29, 32) | 33 (31, 34) |
| *Androstenedione* | 6.61 (4.21, 10.1) | 8.92 (3.22, 11.1)* | 13.9 (8.45, 15.1)* |
| *Allopregnanolone* | 9.59 (5.7, 13.7) | 6.02 (4.01, 8.63) | 11.5 (6.81, 20.6)* |
| *Androsterone* | 0.426 (0.37, 0.671) | 0.405 (0.318, 0.691) | 1.14 (0.638, 1.39)* |
| *5α-Androstane-3α,17β-diol* | 0.464 (0.0321, 0.078) | 0.0392 (0.031, 0.138) | 0.104 (0.0636, 0.124)* |
| *5α-Androstene-3β,7β,17β-triol* | 0.429 (0.0329, 0.0797) | 0.0479 (0.0409, 0.0663) | 0.0802 (0.068, 0.159)* |
| *Estradiol* | 9.89 (6.64, 13.3) | 8.54 (1.15, 14) | 14.7 (12.4, 17.5)* |
| *Estriol* | 90.5 (50.3, 163) | 80.6 (13.3, 98.9) | 161 (67.6, 191)* |
| *Testosterone* | 4.07 (2.39, 5.95) | 4.16 (3.02, 5.3) | 7.45 (5.2, 7.99)* |

Significance level (*) $p<0.05$ Kruskal-Wallis test. Groups did not differ in age. Levels are shown as the median and quartiles in (nM).

**Table 3.** Significant changes in steroid levels related to postpartum mental disorders in mixed umbilical cord blood.

| Variable | Without depression | Mild depression | Moderate depression |
|---|---|---|---|
| *Age* | 33 (29.5, 36.5) | 30 (28.8, 31.3) | 32 (30.5, 33) |
| *Estradiol* | 9.32 (7.45, 18.7) | 19.8 (16.7, 24.8)* | 19 (11.3, 24)* |
| *Estron* | 63.4 (37, 95.7) | 62 (40.2, 152)* | 84.6 (58.4, 105)* |
| *Estriol* | 133 (79.8, 228) | 270 (85.2, 448)* | 297 (173, 314)* |
| *16α-Hydroxy-progesterone* | 77.7 (58.1, 92.9) | 147 (128, 221)* | 175 (126, 205)* |

Significance level (*) $p<0.05$ Kruskal-Wallis test. Mothers did not differ significantly in age. Levels are shown as the median and quartiles in (nM).

## Discussion

The etiology of postpartum depression has not yet been fully elucidated, though a number of theories have attempted to clarify its development. Some authors consider it an autoimmune disease (Gleicher 2007), while others seek genes or other predispositions to this disorder (Mitchell *et al.* 2011, Ptacek *et al.* 2011). Most theories are based on the assumption that pregnancy and subsequent labour leads to dysregulation of the GABAergic system, and search for a cause among the neuroactive steroids (Maguire and Mody 2008).

In our study, we analyzed the entire steroid metabolome at various stages and searched for relations with the development of depression. Sampling of maternal blood was performed four weeks prior to childbirth, at the onset of uterine contractions, after childbirth, six weeks after childbirth and six months after childbirth. We also collected umbilical cord blood. We monitored the mental status of all women using the Hamilton Depression Rating Scale, standardized rating scale. Based on our results, the women were divided into groups according to postpartum depression levels. In our group, there were no women displaying postpartum psychosis, a disease with a different basis than PPD, and therefore not observed within our study. At the same time, no patients with pre-existing psychiatric condition were included in the study, as such patients may develop psychological changes after childbirth for different reasons.

Given the status of steroidogenesis could later be related to changes of a mother's mental state, we attempted to determine which steroids are related to the development of depressive symptoms in the postpartum period. We found that certain changes in steroidogenesis occurring as early as four weeks prior to childbirth could be related to subsequent mental changes. Based on the results shown here and from previous studies (Hill *et al.* 2010a,b), we show that certain androgens and their metabolites, a primary source of which is most likely the mother's adrenal gland and which are further processed in other peripheral tissues especially the mother's liver, are

related to such changes. However, the best relation between steroidogenesis and PPD were steroids from maternal blood in the third stage of labour and steroids from mixed umbilical cord blood. The dominant changes included testosterone in maternal blood and estrogens in mixed umbilical cord blood.

Estrogens affect the mental state and memory through classic monoamine and neurotransmitter receptor mechanisms in the brain, and low estrogen levels are associated with PPD. In addition, estrogens stimulate growth in the number of dopamine receptors, and increase the density of 5-hydroxytryptamine binding sites in brain areas controlling mood, mental state, cognitive characteristics, emotions and behaviour (Fink *et al.* 1996).

Estrogens in rodents also stimulate expression of the arginine-vasopressin gene in the stria terminalis, the area responsible for social and olfactory memory. Described mechanisms suggest a protective role of estrogens (Fink *et al.* 1996), which has been supported by both their positive effects in the treatment of PPD in women (Gregoire *et al.* 1996, Ahokas *et al.* 1999); and the negative effects observed after discontinuation of giving supplemental estrogen to women (Bloch *et al.* 2000). In our study, we found higher estrogen levels in the umbilical cord blood in the newborns of mothers who developed some degree of depression in the postpartum period. We speculate that a more rapid decrease in estrogen levels may play a certain role in the development of mental changes after childbirth.

In terms of steroid biochemistry, it is interesting that the postpartum depressions are related to mainly products of reducing action of 17β-hydroxysteroid oxidoreductases and aldo-keto reductases, clearly both placental (estrogen) and maternal (testosterone). This indicates a possible common genetic basis for this phenomenon.

These results suggest that changes in both maternal and fetal steroidogenesis are involved in the development of mental changes in the postpartum period, and can be used in future as predictive markers of such changes. Our results may help increase our understanding of these changes, but on the other hand lead to various other questions related to this current and very serious problem. In terms of clinical practice, the early prediction of postpartum mental disorders allows treatment to prevent the development of serious mental disorders that can lead to permanent consequences.

## Conclusions

To conclude, we observed in this study changes in the steroid spectrum in relation to developing PPD. We found changes in steroidogenesis related to the development of postpartum depression as early as four weeks prior to childbirth. The best relation between steroidogenesis and PPD were steroids in venous blood in the third stage of labour and steroids from mixed umbilical cord blood. The dominant changes included testosterone in maternal blood and estrogens in mixed umbilical cord blood.

These results suggest that changes in both maternal and fetal steroidogenesis are involved in the development of mental changes in the postpartum period. A description of these changes in relation to postpartum depression can help clarify the causes of this disease. Changes in steroid hormones are thus a promising marker of mental changes in the postpartum period.

## Conflict of Interest

There is no conflict of interest.

## Acknowledgements

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