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# Depression, anxiety, and stress after preterm delivery: role of previous progesterone therapy

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**Summary**

*Purpose of the study:* To determine the influence of progesterone therapy in imminent preterm delivery on early postpartum anxiety, stress, and depression symptoms and to compare the scores of two scales: the Depression, Anxiety and Stress Scale (DASS) and the Edinburgh Postpartum Depression Scale (EPDS) on third day postpartum. *Materials and Methods:* The sample consisted of 37 women on progesterone therapy between 28 and 37 weeks who delivered prematurely. Controls were 40 pregnant women without progesterone therapy who also delivered prematurely. On third postpartum day all participants completed DASS and EPDS. Student's *t*-test (Leven correction for small samples) compared the scores of these two scales. *Results:* The control group showed significantly higher levels of depression symptoms in DASS questionnaire on third day after preterm delivery. Conclusions: Progesterone lowers the intensity of depressive symptoms after preterm delivery. The DASS scoring system was effective in early detection of postpartum depressive symptoms.

*Key words:* Progesterone therapy; Preterm delivery; Postpartum depression.

## Introduction

Imminent preterm delivery is the occurrence of regular contractions (labor) between 20th and 37th week of gestation (calculated from the first day of last menstrual bleeding). In this event fetus is especially at risk because of its low birth weight (between 500 and 2,500 grams) and cardiovascular, respiratory, and thermoregulation instability. Of 11.8% women who deliver prematurely in the USA, 50% are with twins or higher order multiples after use of ovulation induction and assisted reproductive technologies. Thirty-three percent of all preterm deliveries occur after silent infection and/or preterm premature rupture of fetal membranes. Relative risk (RR) is six to eight times higher in multiple pregnancies, or if there is a history of previous preterm delivery. In African-Americans, as well as population groups with low socioeconomic status, the RR is three times higher. Other minor preterm labor risk factors (such as anemia, poor maternal weight gain, smoking, bacterial vaginosis, bacteriuria, and history of uterine abnormality) can compound and, in that way, increase the RR [1]. The fact is that in as high as one-third of all preterm deliveries etiology remains unknown, so we must reconsider one more risk factor- psychology of the pregnant woman as an individual. Stress induces the production of cortisol (in both, maternal and fetal adrenal glands), which consecutively increases levels of placental corticotrophin releasing hormone (CRH). This hormone lowers the local response and protective role of progesterone in the pregnant uteri. On the other hand, productions of estriol (E3) results in myometrial hypersensitivity to oxytocin, regular contractions, and preterm delivery. Measurement of CRH in maternal blood after 18th week of pregnancy predicts preterm delivery [2]. Recent studies confirmed that high levels of anxiety during pregnancy influenced both prenatal and postpartum depression occurrence [3]. Since prenatal depression is a very strong predictor of postpartum depression, it is critical that treatment for depression start prior to delivery [4]. Systemic progesterone administration is one of the approaches to prevention and therapy of postpartum depression [5]. The aims of this study are to determine the influence of progesterone therapy in imminent preterm delivery on early postpartum anxiety, stress, and depression symptoms and to compare the scores of two scales: the Depression, Anxiety and Stress Scale (DASS) and the Edinburgh Postnatal Depression Scale (EPDS) in early detection of depressive symptoms after preterm delivery.

## Materials and Methods

During the study period of eight months (from June 2011 to February 2012), at the Clinic for Obstetrics and Gynecology "(removed for blind review)", authors had collected data from 77 preterm birth records. In this retrospective case-control study the sample consisted of 37 patients who delivered before 37th gestation week after they had received progesterone during their pregnancy. The therapy was either intramuscular injection of 17 alpha-hydroxyprogesterone caproate (17 OHP-C) every five days, or micronized progesterone (P4) capsules, 400-600 mg divided

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Table 1. — *T-test for small independent samples (degree of freedom - df = 75)*

| | Progesterone therapy[a] | No. of participants | Mean | Std. deviation | Std. Error mean | F[c] | Significance (*p*) |
|---|---|---|---|---|---|---|---|
| DASS score anxiety | 0 | 40 | 8.60 | 6.205 | 0.981 | 3.539 | 0.064 |
| | 1 | 37 | 7.00 | 4.403 | 724 | | |
| **DASS score depression** | **0** | **40** | **6.85** | **7.152** | **1.131** | **14.905** | **0.000** |
| | **1** | **37** | **4.76** | **3.883** | **0.638** | | |
| DASS score stress | 0 | 40 | 10.78 | 6.654 | 1.052 | 0.107 | 0.744 |
| | 1 | 37 | 10.59 | 5.909 | 0.971 | | |
| EPDS | 0 | 35[b] | 8.57 | 5.175 | 0.875 | 1.745 | 0.191 |
| | 1 | 37 | 6.92 | 4.078 | 0.670 | | |

Note:
a: Progesterone therapy: not administered - 0 (control); administered - 1 (sample).
b: Five participants of the control group did not fulfil EPDS questionnaire (df =70).
c: F- Empirical value of *t*-test (Levene's Test for Equality of Variances).

into two or three doses every day. Both P4 and 17-OHP-C proved their efficacy in the tertiary prophylaxis of preterm birth after initial 24 hour intravenous tocolytic therapy (with beta-2 agonists) [6]. In the control group, 40 patients did not receive progesterone and also delivered prematurely. The exclusion criteria were: patients under the age of 18, unfamiliar with (removed for blind review) language and writing, patients who had psychiatric disorders diagnosed before pregnancy, and prenatal or neonatal death in actual pregnancy. The Ethical Committee at (removed for blind review) had approved, and all the participants signed a document of informed consent. Information collection was from the patients' records, with clinic's management permission.

The present authors grouped, described, and analyzed data regarding age, education, employment, body mass index (BMI), smoking habit, and healthcare satisfaction. Obstetrical risk factors for preterm birth presented as pregnancy induced hypertension, twin pregnancy, intrauterine growth restriction, preterm premature rupture of membranes (PROM), and placental hemorrhage (preceding placenta and abruption of placenta).

Two questionnaires were translated into local language were the instruments of psychological risk factors measurement: EPDS [7] and the DASS [8].

Participants of the sample and control group answered the ten EPDS and 42 DASS questions on third day after their preterm delivery. The tests were similar also in the symptoms intensity scale (Likert scale: 0, 1, 2 or 3 which indicated how much the statement applied to the patient- 0-did not applied at all; 1-applied to some degree or some of the time; 2-applied to a considerable degree or a good part of time; 3-applied very much or most of the time).

The main difference that gave us the idea for using two parallel tests is that EPDS does not describe somatic symptoms (*breathing difficulty, leg shakiness [("legs going to give way"), difficulty to relax, difficulty in swallowing, sense of heart rate increase, heart missing a beat, sweating, trembling ("in the hands")]* which are present in the early postpartum period and often mask the onset of depression. EPDS [7] is a screening instrument acknowledged worldwide. Cox and Murray modified the EPDS and created Edinburgh Depression Scale-EDS [7] for measuring of depression symptoms during the third trimester of pregnancy and early postpartum period. The EDS score higher than 14 points confirms the presence of depression. DASS contains three groups of questions (14 each) about the symptoms of anxiety, depression, and stress. Depression is present if the score is higher than 28, more than 20 points confirm anxiety, and score that is higher than 34 confirms the presence of severe stress [8].

Statistical software (SPSS 17th version) used *t*-test for two small independent groups of participants. Graphical presentation described main results and significance of difference between the sample and control.

## Results

Main demographic characteristics: maternal age, education, employment, body mass index, smoking, and healthcare satisfaction, were similar in the sample and control. Maternal age did not defer significantly (mean 31.6 (SD 5.5) in the sample and 30.43 (SD 5.9) in control); time of preterm delivery was around 34th gestation week (33.6 (SD 2.6) in the sample and 34.0 (SD 2.3) control). Mean parity was 1.25 both in the sample and control. Other observed risk factors (pregnancy induced hypertension, twin pregnancy, intrauterine growth restriction, and placental hemorrhage) were equally present in both groups. Nevertheless, the PROMs showed higher prevalence in the study (32, 5 %) than in the control (22, 2%) group. Table 1 represents the means and significance of difference in DASS and EPDS scores between the sample and control. There was no statistically significant difference in both DASS anxiety and stress scores (degree of freedom- df = 75, 95% CI). Mean EPDS scores showed no statistical significance, but seven (20 %) women of the control group and three (8.1%) of the sample scored above 13. Five participants of the control group did not fulfill the EPDS questionnaire. Figure 1 ("progesterone therapy and psychology after preterm delivery") shows that, in the control group, there were significantly higher levels of depression symptoms in DASS questionnaire (95% CI, $p < 0.01$).

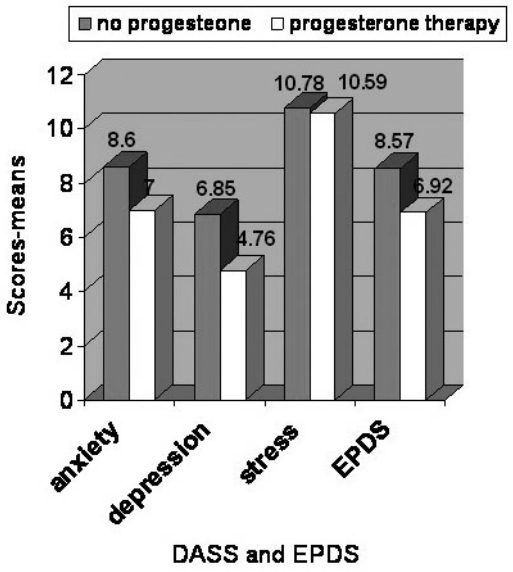


Figure 1. — Progesterone therapy and psychology after preterm delivery.

## Discussion

Straub *et al.* in their study showed a significant relationship between antenatal depressive symptoms and preterm birth. It was independent of maternal age, race/ethnicity, prior preterm delivery, and insurance status [9]. On the other hand, Benute *et al.* investigated the prevalence of major depression in pregnant women with medical disorders. They found it especially high in preeclampsia (7.1%), cardiac disorders (12.1%), and threatened preterm delivery (12.5%) [10]. EPDS cannot distinguish physical (psychophysiological) symptoms that are present in the early postpartum period. After delivery of the placenta, rapid decrease of progesterone and estrogen levels result in physical (involution of genital organs, cardiovascular, and renal redistribution of body liquids and proteins, the onset of lactation), as well as psychological changes. These symptoms often overlap after preterm birth induction in high risk pregnancies. This study investigated the DASS questionnaire as an appropriate instrument in the evaluation of depression, anxiety, and stress symptoms after preterm birth. S.H. Lovibond and P.F. Lovibond had developed this measure in order to assess the full range of anxiety and depressive symptoms. Attempting to provide maximum discrimination between the two scales, they noticed that the third factor-stress had emerged from the items related to difficulty relaxing, irritability, and agitation. DASS questionnaire strongly supported the consistency, convergence, and discriminating validity of the three scales: depression, anxiety, and stress [8]. There are complex environmental, emotional, and physical demands a new mother faces after preterm delivery. According to the results of this study, on third postpartum day, DASS could measure the anxiety, depression, and stress as well as recognize women with depression symptoms.

Progesterone, as the principal steroid hormone of pregnancy maintenance, has its well defined roles. As pregnancy advances, it relaxes the uterine muscle and thickens the mucus cloth in the cervix, thus preventing intrauterine infection, premature labour, and preterm delivery. Through genomic mechanisms that last from minutes to hours, progesterone regulates gene expression in the nuclei of uterine smooth muscle cells. Allopregnanolone, a metabolite of natural progesterone, acts as a neurosteroid. It alters neuronal excitability in the central nervous system through a membrane bound-Gama amino butter acid (GABA-A) receptor, via a non-genomic mechanism [11]. This event occurs in several milliseconds to seconds. At higher doses, neurosteroids may have anxiolytic, anti-aggressive, sedative, and anti-epileptic effects in both animals and humans. During late pregnancy in rats, allopregnanolone modulates hypothalamic-pituitary axis (HPA) responses to stressful stimuli [12]. The progesterone treatment of postpartum depression still remains controversial. Hilgers *et al.* showed that therapy with natural progesterone after birth had significantly decreased number and intensity of all depression symptoms: fatigue, crying, anxiety, helplessness, strange thoughts, reduced appetite, and night sweats [5]. On the other hand, synthetic progesterone used as contraception method during breast feeding increased the RR of postpartum depression, which was 2.56 in comparison to the placebo group [13].

## Conclusions

The use of a small and convenient sample of women from a mostly Caucasian area of Europe limits this study to be generalized. However, the large comeback of therapy with natural progesterone raises the topic of its influence on psychological status of mothers after preterm deliveries. Future randomised studies of depression during pregnancy and postpartum should include more subjects and investigate the real enrolment of progesterone and its metabolites.

## References

[1] Guinn D.A., Gibbs R.S.: " Preterm labour and delivery". *In:* Scot R.J., Gibbs R.S., Karla B.Y. (eds). *Danforths obstetrics and gynecology.* 9th ed. Philadelphia PA: Lippincott Williams & Wilkins, 2003, 173.

[2] Smith R, Smith JI, Shen X, Engel PJ, Bowman ME, McGrath SA, et al.: "Patterns of plasma corticotrophin-releasing hormone, progesterone, estradiol and estriol change and the onset of human labor". *J. Clin. Endocrinol. Metabol.*, 2009, *94*, 2066

[3] Correia L.L., Linhares M.B.M.: "Maternal anxiety in the pre- and postnatal period: a literature review". *Rev. Lat. Am. Enfermagem.*, 2007, *15*, 677.

[4] Beck C.T.: "Predictors of postpartum depression: an update". *Nurs.*

*Res.*, 2001, *50*, 275.
[5] Hilgers T.W.: "Postpartum depression". *In: The medical and surgical practice of NaProTECHNOLOGY*. Omaha: Pope Paul VI Institute Press, 2006. 377.
[6] Borna S, Sahabi N.: "Progesterone for maintenance tocolytic therapy after threatened preterm labor: a randomized controlled trial". *Aust. N. Z. J. Obstet. Gynaecol.*, 2008, *48*, 58-63.
[7] Cox J., Holden J.: "Antenatal research and the EPDS". *In:* Cox J., Holden J.: "Perinatal mental health: a guide to the Edinburgh Postnatal Depression Scale (EPDS)". London: Gaskell, 2003, 29.
[8] Lovibond P.F., Lovibond S.H.: "The structure of negative emotional states: comparison of the Depression anxiety stress scales (DASS) with the Beck depression and anxiety inventories". *Behav. Res. Ther.*, 1995, *33*, 335.
[9] Straub H., Adams M., Kim J.J,. Silver R.K.: "Antenatal depressive symptoms increase the likelihood of preterm birth". *Am. J. Obstet. Gynecol.*, 2012, *207*, 329.e1.
[10] Benute G.R.G., Nomura R.M.Y., Siracuza R.J., Fraguas R. Jr., Lucia M.C.S., Zugaib M.: "Depression during pregnancy in women with a medical disorder: risk factors and perinatal outcomes". *Clinics*, 2010, *65*, 1127.
[11] Wang M.: "Neurosteroids and GABA-A receptor function". *Front. Endocrinol. (Lausanne)*, 2011, *2*, 44.
[12] Brunton P.J., Russell J.A.: "Allopregnanolone and suppressed hypothalamo-pituitary-adrenal axis stress responses in late pregnancy in the rat". *Stress*, 2011, *14*, 6.
[13] McCoy S.J.B., Beal M., Shipman M., Payton M.E., Watson G.H.: "Risk factors for postpartum depression: a retrospective investigation at 4-weeks postnatal and a review of the literature". *J. Am. Osteopath. Assoc.*, 2006, *106*, 193.

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