

The relationship between labor pain management, cortisol level and risk of postpartum depression development: a prospective nonrandomized observational monocentric trial

Oksana V. Riazanova¹, Yurii S. Alexandrovich¹, Alexander M. Ioscovich²

¹ Department of Anesthesiology and Intensive Care, Saint-Petersburg State Pediatric Medical University, St. Petersburg, Russia

² Department of Anesthesiology, Perioperative Medicine and Pain Treatment, Shaare Zedek Medical Center; Hebrew University, Jerusalem, Israel

Abstract

Postpartum depression (PPD) is the main psychological status disorder and women suffering from postpartum depression often need long-term psychological and socio-economic rehabilitation. The study is dedicated to the evaluation of the role of labor pain management using epidural analgesia in natural delivery on stress level in labor and frequency of postnatal depression.

Materials and methods: 210 women were investigated and divided into two groups. In the first group for labor pain management in natural delivery, patient-controlled epidural analgesia was used (bolus - 10.0 - 0.08% ropivacaine hydrochloride, lockout - 30 min, limit - 120 ml/6 h) with a background of continuous-flow infusion of local anesthetic 0.08% ropivacaine hydrochloride solution. Patients in the second group had no pain relief in delivery. The stress level was evaluated using blood plasma cortisol level in the early stages of labor, 6 hours and 3 days after delivery. The assessment of depression development was carried out step-by-step: Before the delivery, 6 hours after, 3 days and 6 weeks after the delivery.

Results: The baby blues frequency 6 hours after the delivery in the group where the pain relief was conducted was 29.91%, with cortisol level below and equal to 2310.91 nmol/l. In the group with no pain relief 6 hours after delivery, baby blues was found in 15.53% of puerperas ($p < 0.05$) and the cortisol level was 2673.82 nmol/l ($p < 0.05$). Six weeks after the birth, postpartum depression was diagnosed in 4.67% of women who received epidural analgesia during delivery, in comparison to 6.79% with no pain relief during delivery. However, the difference was not statistically significant ($p < 0.05$).

Conclusions: The use of epidural analgesia leads to a significant reduction of pain syndrome and stress response during natural delivery, increases the risk of baby blues in the early postnatal period, but slightly influences the frequency of postpartum depression.

Keywords: postpartum depression, baby blues, epidural analgesia, natural delivery, stress, cortisol

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Introduction

Postpartum depression (PPD) is a principal psychological status disorder [1, 2]. According to various

authors, the frequency of the PPD varies from 12 to 20% puerperas, reaching 60% [3-5]. PPD occurs as a constant fatigue, sadness, psychic tension [6-8] and consequently can affect the health of women and their children in the long run [9]. Women suffering from postpartum depression often need long-term psychological and socio-economic rehabilitation [10, 11].

One of the risk factors in PPD development is baby blues in the early postnatal period, which manifests as

Address for correspondence: Alexander M. Ioscovich
str. Hakfir 159
Jerusalem, Israel
E-mail: aioscovich@gmail.com

a disorder of psycho-emotional state, and clears up without pharmacological therapy in 7-10 days after delivery [12-14].

Depression in the perinatal period can be caused by a variety of factors including past stressful life events, lack of partners support during pregnancy, obstetric complications, young age, unintended pregnancy, low socioeconomic status [15-20]. Moreover, pathophysiological mechanisms underlying depression have been discussed [19].

Much attention is given to endocrine factors associated with the pathophysiology of depression development, including the hypothalamic-pituitary-adrenal axis [21, 22]. Physiological hormone changes occur during pregnancy: the concentration of cortisol starts to increase after conception, progressively growing more than twice throughout the whole pregnancy, reaching its peak by the end of the third trimester [23-29]. This hyperactivity is partly related with the increasing level of circulating corticotrophin, that releases placental hormones [20, 30]. After the placenta delivery, the level of cortisol is reducing, reaching the initial levels in 2 weeks after delivery [10, 20, 21, 31-33]. It was suggested that the disruption of the hypothalamic-pituitary-adrenal system functioning may lead to the development of depressive disorders [21, 30, 33-39].

It has been proven that increasing concentration of the stress key marker which is cortisol in the blood plasma of patients is directly related to the increasing depression rate in the overall population [40-43].

On the contrary, when examining the correlation of cortisol with the development of depressive symptomatology in obstetrics, contradictory data was obtained. Some studies have shown that increasing the level of cortisol in pregnancy results in more frequent development of PPD [20, 44-46] and the baby blues [47-51]. In other studies that association was not confirmed [21, 25, 38, 52-61]. Some authors conversely point to higher frequency of PPD at a low level of cortisol after delivery [62-64].

Recently, studies on the association between labor pain relief using epidural analgesia (EA) and the development of postpartum depression are appearing. Data from these studies show a significant decrease in the frequency of postpartum depression among women who received EA during delivery in comparison to those who had no pain relief during the delivery [65-68].

Up to the present moment, the question remains: if the blood plasma cortisol level could be related to the risk of postpartum depression among women who received epidural analgesia during delivery in comparison to puerperas with no pain relief during delivery.

Materials and methods

Following the approval of the Ethical Committee, a clinical-and-psychological examination of 210 women was conducted. All women were applied electively in the Perinatal Center of the Saint-Petersburg State Pediatric Medical University from December 2015 to March 2017, at the gestational age 34-35 weeks. Patients were offered to participate in the study. After signing informed consent to participate in the study, pregnant women completed the clinical questionnaire for neurotic states identification and evaluation [69].

To evaluate the stress level during the delivery, cortisol level in venous blood plasma during early labor stage, 6 hours after and 3 days after was measured. Taking into the consideration the physiologic diurnal cortisol level variations [33, 70], the first and third blood samples were collected in the morning hours (7-9 hours). Immunoenzymatic test kit (Alkor Technologies, Saint-Petersburg, Russia) was used for cortisol level evaluation. The optical density was measured using a photometer of vertical scanning Labsystems Multiskan IUS/340, Finland, wavelength 450 nm.

During the delivery, the pain was assessed using the visual analog scale (VAS). In the postpartum period 6 hours, 3 days and 6 weeks after the delivery, the patients completed the Edinburgh Postnatal Depression Scale [71, 72]. Based on Mazo et al. (2012) study results, postpartum depression was identified with a score equal to 10 points or higher, which indicates the probability of postpartum depression [73].

All patients were divided into 2 groups, depending on the request of the women for pain relief during delivery using epidural analgesia method. In the first group, at the request of the patients, natural delivery was carried out with epidural analgesia, puncture and epidural space catheterization was conducted in the presence of regular labor activity. Patient-controlled analgesia was conducted (bolus - 10.0 - 0.08% of ropivacaine hydrochloride solution, lockout - 30 min, limit - 120 ml/6 h) with a background continuous-flow infusion of 0.08% ropivacaine hydrochloride solution at a speed of 10 ml/h. In the 2nd group, women at the natural delivery were not receiving any analgesia as they were primed for delivery with no pain relief.

The criteria for exclusion from the study included severe somatic pathology, psychiatric disorders in the decompensation stage, purulent-septic diseases, allergy to local anesthetics, and the presence of coagulopathy or systemic treatment with anticoagulants.

The questionnaire was processed and evaluated by a psychologist who was not present at the delivery and had no information regarding the method of pain relief in delivery.

The statistical processing of the data was carried out using the STATISTICA v. 7.0 (STATCON, Witzhausen, Germany) software packages using non-parametric tests (Wilcoxon test), as part of the data set did not comply with the normal distribution law. The initial results of the study are presented as a median, 25 and 75 percentiles. The critical significance value is set to $p < 0.05$.

Results

The general characteristics of the patients surveyed are presented in Table 1. During the examination of patients, no significant difference in age and anthropometric indexes was identified in the groups studied. The age of women in first group was 29.28 (26-31) years, the age of women in second group - 30.02 (27-32) years. The body weight of women in the first group was 73.66 (65.85-78.5) kg, in second group - 71.5 (68-77.4). Gestational period - 39.72 (39.5-40.5) and 39.74 (39.5-40.5) weeks respectively. However, there was no statistically significant differences between the groups ($p > 0.5$). The condition of newborn babies at birth was also not significantly different between groups, 1 min after birth the average Apgar score was 7.8 (8-8), 5 min after - 8.9 (9-9) ($p > 0.5$).

The results of the pain assessment during the delivery using VAS are presented in Table 2, which

shows that the expression of pain syndrome during the cervical dilatation 5 cm and in the active pushing phase was significantly higher in patients with no pain relief, pain rates were 6.96 and 8.26 respectively in comparison to 2.5 and 4.76 in puerperas receiving EA, what was statistically significant ($p < 0.05$). On the early stage of labor (when cervical dilatation is 2-3 cm), the highest ratings on the VAS scale were obtained from the patients in the first group and were 8.6 points compared to 4.7 in the second group, the difference was statistically significant ($p < 0.05$).

Blood cortisol level assessment in women in the early stage, 6 hours and 3 days after delivery, is presented in Fig. 1. In the early stage of labor, prior to epidural analgesia, the cortisol level did not differ between the groups and was 2485.54 nmol/l and 2476.54 nmol/l in the first and second groups respectively ($p > 0.05$). Six hours after the delivery, cortisol level in blood plasma decreased to 2310.91 nmol/l in women receiving EA compared to 2673.82 nmol/l in patients with no pain management. Presented difference was statistically significant ($p < 0.05$). Three days after the birth, it was determined that there was no statistically significant difference of cortisol level in blood plasma of puerperas, which was 2197.46 and 2161.18 nmol/l in the first and second groups respectively ($p > 0.05$).

The assessment of the depression of women, depending on the usage of analgesia in delivery, is

Table 1. The general characteristics of the patients

Data	Epidural group (n = 107)	Nonepidural group (n = 103)	p
Age, years	29.28 (26-31)	30.02 (27-32)	0.081209
Height, cm	166.6 (163-170)	166.5 (163-170)	0.812380
Weight, kg	73.66 (65.85-78.5)	71.5 (68-77.4)	0.422001
Gestation age, weeks	39.72 (39.5-40.5)	39.74 (39.5-40.5)	0.130570
Apgar, 1 min	7.82 (8-8)	7.84 (8-8)	0.802587
Apgar, 5 min	8.93 (9-9)	8.98 (9-9)	0.683091

Table 2. The results of the pain assessment during the delivery using VAS

Data	Epidural group (n = 107)	Nonepidural group (n = 103)	p
VAS, cervical dilatation 2-3 cm	8.6 (8-10)	4.7 (4-6)	0.000000
VAS, cervical dilatation 5 and more cm	2.5 (2-3)	6.96 (6-8)	0.000000
VAS, second stage of labor	4.76 (4-6)	8.26 (8-9)	0.000000

VAS = visual analog scale

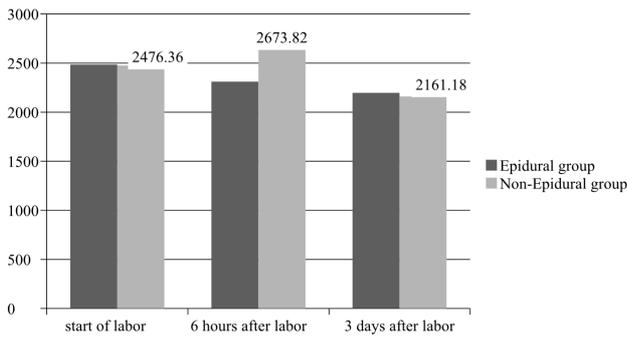


Fig. 1. Blood cortisol level assessment in women in the early stage, 6 hours and 3 days after delivery ($p < 0.05$ 6 hours after labour)

presented in Fig. 2. The initial psychological status did not vary significantly between the groups. In the third trimester of pregnancy, depression was registered in 17.76% of women in first group and 19.42% of second

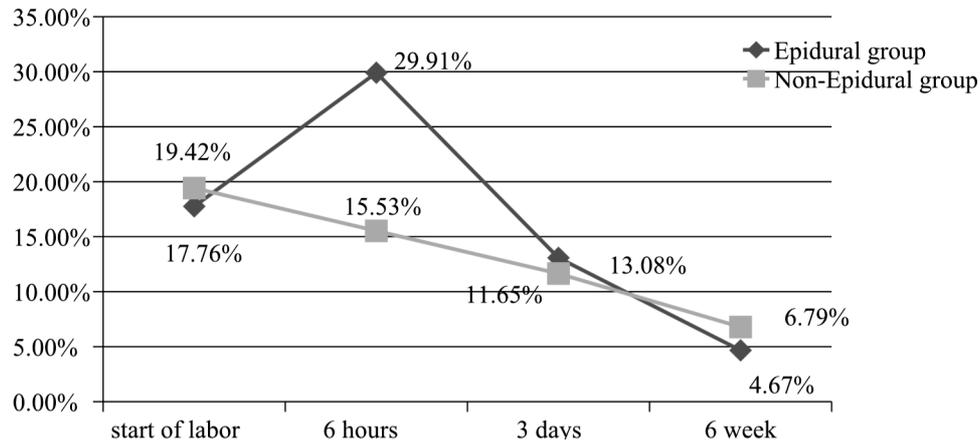


Fig. 2. The assessment of the depression of women, depending on the usage of anesthesia in delivery ($p < 0.05$ at 6 hours)

group ($p > 0.05$). 6 weeks after delivery, the PPD was diagnosed in 5 out of 107 women (4.67%) who received epidural analgesia in delivery and in 6 of 103 puerperas (6.79%) with no pain relief during delivery, but the difference was not statistically significant ($p > 0.05$).

Six hours after the delivery, the baby blues rate was significantly higher in puerperas, who received continued epidural analgesia in labor and was diagnosed in 32 women (29.91%) compared to 16 (15.53%) who did not receive pain relief in labor ($p < 0.05$). The cortisol level was significantly lower in the EA group compared to the group with no pain relief ($p < 0.05$). For the third day after the delivery, the statistically not significant difference in the baby blues rate was 13.08% and 11.65% in the first and second groups respectively ($p > 0.05$).

In the study of the cortisol level influence on the baby blues development 6 hours after the delivery, a negative correlation was detected; however, the

relationship was not statistically relevant ($r = -0.1771$, $p > 0.05$), as shown in Fig. 3. 6 hours after the delivery in puerperas that received EA, the cortisol level was decreased to 2310.91 nmol/l compared to 2673.82 nmol/l in women with no pain relief ($p < 0.05$). This led to a baby blues frequency increase, which developed in 29.91% of women after analgesia, compared to 15.53% with no analgesia ($p < 0.05$). However, this did not significantly affect the development of postpartum depression 6 weeks after delivery, which was registered in 4.67% of women who received pain relief in delivery compared to 6.79% with no analgesia ($p > 0.05$).

Discussion

For most women, childbirth is inevitably associated with severe pain and stress, which are considered to be among the key factors of PPD development. The

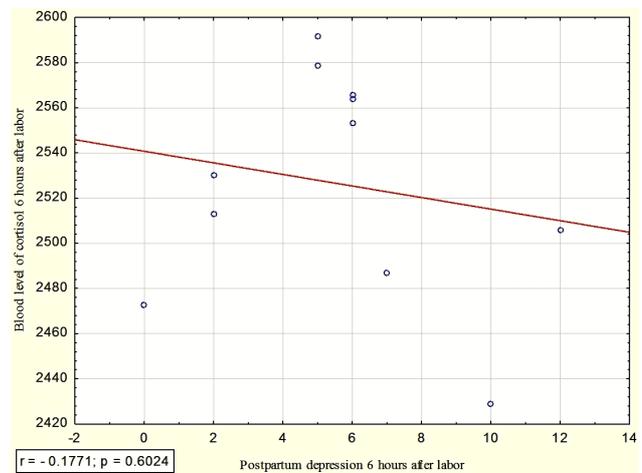


Fig. 3. The correlation between blood cortisol level and the baby blues development

overwhelming majority of puerperas described the pain suffered in childbirth as one of the worst experiences

they had throughout their lives [33, 41, 74]. Up to 60% of primiparas describe the pain in childbirth as “severe” or “very severe” [74].

Previous studies have shown that the pain in childbirth correlates with the development of depressive disorders. Boudou et al. in 2007 and Eisenach et al., in 2013, reported that the severity of pain in delivery was related to the risk of mood disorders during the postnatal period or depression [75, 76]. In 2008, Eisenach et al. analyzed 1228 deliveries in the United States and found that every 5th woman after caesarean section and every 13th woman during natural delivery suffered severe acute pain [77]. At the same time, the severity of the suffered severe pain was an independent factor for chronic pain and depression risk. The study by Soet et al. (2003) revealed a close relationship between the intensity of the pain in childbirth with post-traumatic stress and the mood disorder in the early postnatal period [78]. According to data, chronic pain syndrome after natural delivery ranges from 1% to 10% [76, 79].

Our study has shown less expressed pain syndrome and stress in the case of pain relief through epidural analgesia, which is characterized by lower ratings in VAS and lower cortisol levels. But this did not have a significant impact on the risk of postpartum depression six weeks after delivery, which was recorded in 4.67% of women that received EA in comparison to 6.79% with no anesthesia ($p > 0.05$). Previous studies have shown a significant reduction of postpartum depression frequency in puerperas who received the EA during the delivery. Ding et al. (2014) reported the frequency of the PPD, 6 weeks after delivery, in 14% of women who received EA, compared to 24.3% with no analgesia [66]. Thangavelautham et al. (2016) found PPD development in 10% of puerperas who received EA, in comparison to 19.3% with no analgesia in delivery [67]. Orbach-Zinger et al., in 2017, also described the decrease of postpartum depression frequency 6 weeks after the delivery according to the Edinburgh Postnatal Depression Scale [68].

A direct correlation [40, 42, 43] is demonstrated in studies of cortisol level effects on depressed state development in non-pregnant patients. Some authors suggested using the assay of salivary cortisol level in morning hours as a biomarker for the development of depressive episodes arising in the first year after the assessment of cortisol [80, 81, 83].

Conflicting results have been obtained in obstetrics. Stavros et al. (2015) showed a statistically higher rate of depression development in the postnatal period with higher concentrations of salivary cortisol ($p = 0.166$, $p < 0.05$). In two studies it is shown that conversely, lower cortisol levels result in the depression development in the postnatal period [22, 33, 34, 84-86].

Recently, studies of depressive states development depending on the suffered stress and cortisol level have been published [29, 87, 88]. However, we did not find studies on the relationship of the pain management of delivery with the cortisol level and the frequency of the PPD. As far as we know, this study is the first one on this topic.

In our study, 6 hours after the delivery baby blues was found significantly more often (29.91%) with a lower blood plasma cortisol level (2310.91 nmol/l) in patients of the first group, where EA was used for analgesia in labor, in comparison to 15.53% that had no analgesia, while their concentration of cortisol was significantly higher (2673.82 nmol/l) ($p < 0.05$). This result can be explained by the direct influence of the epidural analgesia in childbirth on the stress reaction of the body, accompanied by a decrease blood plasma cortisol level and inversely proportional frequency of postnatal blues development 6 hours after the delivery. 3 days after the delivery, there was also a difference in the frequency of the baby blues, which was registered in 13.08% of the first group, in comparison to 11.65% of the second group, but the difference was not statistically significant ($p > 0.05$), wherein there was no difference in cortisol level in both groups. This result had a small impact on the frequency of the PPD in 6 weeks after delivery.

Our results contradict previous studies. Taylor et al. (2009) in their study showed a higher level of cortisol in women with clinical characteristics of postnatal blues and PPD [46]. Similarly, Okano et al. (1992), Lommatzsch et al. (2006) described that women with postnatal blues had a higher level of serum cortisol on the third and fourth day after delivery in comparison to healthy puerperas [44, 49]. Pedersen et al. (1993) found that women suffering from depression six weeks after delivery had significantly higher levels of serum cortisol in the morning hours [50].

On the other hand, the opposite results are shown in a number of studies. For example, Saleh et al. (2013) showed lower cortisol levels in the postnatal period for women suffering from PPD compared to healthy puerperas [64]. Groer and Morgan (2007) found a negative associative relation between the postpartum depression and the salivary cortisol level [63]. Finally, a number of studies assessing the cortisol level in relation with postpartum depression symptoms showed a minor correlation [22, 56-59, 89]. This work has one main limitation which is a lack of randomization, though it is impossible to decide whether a patient will receive epidural or not only for the sake of randomization. We plan to carry out a similar study in a number of different centers as soon as possible for additional information regarding the correlation between stress and a risk of PPD.

Conclusions

Continuous epidural analgesia use in natural delivery has led to a reduction in the pain syndrome intensity in labor, and reduced the concentration of cortisol in the early postnatal period. However, an increase in the frequency of postpartum blues occurred on the first day after delivery. Adequate pain relief of delivery had a small impact on the postpartum depression frequency six weeks after delivery.

Conflict of interest

Nothing to declare

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