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Research Paper:

The Relationship Between Delivery Mode and Cord Blood Betaendorphins Values in the Newborns of Nulliparous Women

Shahnaz Tork-Zahrani[1], Farahnaz Heshmat[2*], Hanieh Abbasinia[3], Hossein Delshad[4], Nezhat Shakeri[5], Mahboobeh Valiani[2]

1. Department of Midwifery, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Department of Midwifery, School of Nursing and Midwifery, Isfahan University of Medical Sciences, Isfahan, Iran.
3. Department of Midwifery and Reproductive Health, School of Nursing and Midwifery, Tehran University Medical Science, Tehran, Iran.
4. Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
5. Department of Biostatistics, School of Par Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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ABSTRACT

Background & Aims of the Study: Beta-Endorphin (β-EP), as the main stress hormone, is secreted during delivery and labor and modifies the pain threshold and sensation. This study aimed to determine the umbilical cord blood level of β-EP and its related factors in two groups of nulliparous women with Natural Vaginal Delivery (NVD) and Elective Cesarean Section (ECS).

Materials and Methods: This case-control study was conducted on 80 pregnant women (40 cases & 40 control) at 38-42 weeks of gestation. Besides, the study subjects presented no history of chronic diseases, pregnancy complications, abortion, stillbirth, or infertility. The explored cases were women with NVD and the control were women with ECS. After delivery, a 3-mL blood sample was collected from the placental umbilical cord. After separating the blood serum, the β-EP level was examined using a standardized β-EP kit (Glory Co., USA). Data analysis was performed in SPSS using the Chi-squared test, t-test, and Fisher's Exact test ($P \leq 0.05$).

Results: The study groups were matched on individual, social, and obstetric characteristics, such as age, educational level, occupational status, gestational age, body mass index, and the frequency of prenatal care. The obtained results indicated that the umbilical cord blood levels of β-EP were significantly higher in the NVD group, compared to the ECS group ($P=0.03$).

Conclusion: The present research results suggested that NVD provides greater effects on the release of β-EP, in comparison with ECS.

*** Corresponding Author:**
Farahnaz Heshmat, MD.
Address: *Department of Midwifery, School of Nursing and Midwifery, Isfahan University of Medical Sciences, Isfahan, Iran.*
Phone: *+98 (31) 46259061*
E-mail: *farahnaz.h@hotmail.com*

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1. Introduction

Endorphins are recognized as peptides, i.e., naturally secreted from the anterior pituitary gland in response to exercise and biopsychological stress. These conditions increase the plasma level of Beta-Endorphin (β-EP), i.e., a stress hormone similar to cortisol and catecholamine [1]. Generally, β-EP is described as the main endorphin released in the blood. It is an opioid peptide derived from Proopiomelanocortin (POMC), i.e., a precursor of Corticotropin-Releasing Hormone (CTRH), concurrently changing with β-EP [2]. Adenohypophysis was reported as the major source of β-EP [3].

Evidence suggests that endogenous opioid peptides affect responses to various stressors [4]. These peptides may also reach the Central Nervous System (CNS) through the blood-brain barrier. They might produce analgesia by binding to opioid receptors at both pre- and post-synaptic nerve terminals. They primarily exert their effects through presynaptic binding [5] and contribute to the modulation of pain perception [6]. In addition to its opioid function, β-EP is involved in various physiological processes [7], including the regulation of immune and reproductive systems [8]. Moreover, another function of β-EP is to reduce pain perception and discomfort experienced by the fetus during delivery [4]. β-EP in the umbilical cord plasma mostly stems from the fetal pituitary glands and is synthesized and secreted by other organs, including the placenta. Overall, the complete pituitary function is required for normal fetal growth and development. Besides, a high level of β-EP, regardless of delivery stress, presents direct effects on the neonate's movements and development [9].

Parturition and delivery are particularly stressful events for mothers and neonates [10]. The POMC derivatives may be involved in maternal and fetal adaptation mechanisms in exposure to these stressful conditions [11]. Opioid peptides in the CNS lead to an increase in the pain threshold during labor. Additionally, opioid activity is enhanced in the CNS. Several researchers have reported elevated concentrations of β-EP in the peripheral plasma of women during parturition [12, 13]. Considering that β-EP is an opiate-like compound, it may be responsible for pain tolerance [14].

The plasma level of β-EP significantly decreases at gestational weeks of 28 and 33, compared to the tenth week of gestation, followed by an increase between gestational weeks 28 and 37. However, there is no change in the level of β-EP between gestational weeks 10 and 37 [15]. Moreover, the plasma levels of β-EP are elevated after vaginal delivery, and the differences are significant [16].

According to studies, neither uterine contractions nor the mode of delivery and anesthesia [17] can affect the umbilical cord plasma levels of β-EP in human neonates [18]. Furthermore, some studies revealed that Elective Caesarean Section (ECS) is less stressful for the fetus than Natural Vaginal Delivery (NVD) [19]. Besides, the cord blood levels of cortisol, β-EP, and catecholamine are much lower in this case [20]. Considering the essential effects of β-EP on maternal and neonatal outcomes, besides the scarcity of research and contradictory results on β-EP secretion, this study aimed to investigate the relationship between the mode of delivery and the umbilical cord blood levels of β-EP in newborns.

2. Materials and Methods

This case-control study was conducted on 80 pregnant women 40 cases &d 40 control), referring to Shahid Beheshti Hospital in Isfahan City, Iran. The sample size was determined according to the literature [21] after consultation with a statistician at a confidence interval of 95% and odds ratio of 5%. The selected samples were then divided into two groups. The research project was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (Code: Sbmu.rec.1392.284).

The explored women were first informed about the study objectives and methods and then requested to provide a written informed consent form if willing to participate in the study. The inclusion criteria were as follows: an age range of 18-35 years (Mean±SD = NVD: 25.14±3.60, ECS = 24.66±4.34 y), Iranian nationality, primiparity with a term pregnancy (gestational age: 38-42 weeks), and singleton and uncomplicated pregnancies (the lack of diabetes, blood pressure disorders, & endocrine disorders). Chronic and endocrine diseases might affect the level of β-EP; thus, they were included in this study to eliminate the risk factors for pregnant women without the disease, who had an intact amniotic sac.

On the other hand, the exclusion criteria were unwillingness to participate in the study; problems interfering with the NVD process and leading to ECS (disturbances in dilatation & descent); major health problems, such as abortion, fetal death, and infertility; the use of medications; heavy drinking and substance abuse, and the use of hormones during pregnancy (except for vitamins).

The required data were collected using a demographic and obstetric questionnaire. The validity of the first questionnaire was examined using the content validity method by an expert team. The study population consisted of 40 mothers with NVD, as well as 40 women who delivered via ECS without a trial of labor. One to two minutes after delivery, after clamping the fetal umbilical cord, because of the negligible difference in the mean of beta-endorphin in arterial and venous blood, mixed umbilical cord blood samples were collected from the placental umbilical cord in 3-mL plastic syringes when the cord was clamped and cut. All the collected blood samples were placed in ice-cold siliconized glass tubes, containing Edetate Disodium (EDTA) and bacitracin.

The collected specimens were immediately centrifuged at 3000 rpm for 30 minutes at 4°C. Besides, the supernatant plasma was transferred to ice-cold siliconized glass tubes. They were then immediately frozen and stored at -75°C until further assays. After collection, the plasma was tested within 3 months using relevant kits (Glory Biotechnology Co.; USA). The kit (ISO9001) was calibrated according to the World Health Organization (WHO) guidelines for β-EP level. The reliability of the β-EP kit was measured in the absorption spectrum of 450 nm. The level of β-EP was measured using a highly specific radioimmunoassay, which included an analytical saturation method of radioimmunoassay; the results were then averaged [21].

After sampling and measuring the level of β-EP, a boxplot chart was drawn. Considering the presence of five data in the chart, data related to 5 samples (3 samples from the NVD group & 2 samples from the ECS group) were omitted. After the studies, it was found that the results of the data were in the process of testing and laboratory error. Finally, 38 women were assigned to the NVD group, and 38 women were assigned to the ECS group.

For data analysis, SPSS was used. Descriptive statistics, including central tendency, dispersion, and frequency distribution, were measured to describe the research groups. Chi-squared test and Fisher's Exact test were applied to compare qualitative variables between the study groups. Moreover, quantitative variables were compared using Independent Student Samples t-test. Finally, the Kolmogorov-Smirnov test was performed to examine the normal distribution of the achieved data. P≤0.05 was considered statistically significant.

3. Results

Totally, 80 pregnant women with the Mean±SD age of 24.89±4.12 years were assessed in this study. The research groups were matched by age and occupational status. In total, 71(88.75%) of the study subjects were housewives and only 9(11.25%) mothers were employed.

The Mean±SD Body Mass Index (BMI) and frequency of prenatal care in the studied mothers equaled 23.74±3.65 kg/m^2 and 8.49±2.80 times, respectively. Additionally, the Apgar score of neonates was measured in the study groups.

Table 1. The individual and social characteristics of primiparous women

Variables		Mean±SD/No.(%)		P
		NVD	ECS	
Maternal age, (Year)		25.14±3.60	24.66±4.34	0.28
Education	Primary and secondary school	6(15.0)	5(12.5)	0.93
	High school diploma	18(45.0)	20(50.0)	
	University	26(40.0)	15(37.5)	
Gestational age, (Week)		38.57±0.60	38.37±0.58	0.16
Profession	Housewife	36(90.0)	35(87.5)	0.47
	Employee	4(9.0)	5(12.5)	
BMI before pregnancy		23.82±3.91	23.68±3.31	0.87
Frequency of prenatal care		8.46±2.84	8.53±2.75	0.96

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Table 2. Umbilical cord blood β-EP concentrations and mode of delivery

Variable	Mean±SD		P
	Vaginal delivery (n=37)	Cesarean section (n=38)	
β-EP (ng/l) (Minimum value)	0.1	0.1	------
β-EP (ng/l) (Maximum value)	100	72	------
β-EP (ng/l)	38±27.47	27.11±19.59	0.03
Apgar Score of neonates at 5th minutes	9.55±0.35	9.46±0.32	0.879

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Based on the Chi-squared and Student's t-test data, there was no significant difference between the research groups regarding individual, social, or obstetric characteristics, such as age, educational level, occupational status, gestational age, BMI, and frequency of prenatal care (Table 1). Based on the obtained findings, β-EP level (ng/L) was significantly higher in the NVD group, compared to the ECS group (P=0.03). Moreover, the Mean±SD Apgar score of neonates in study groups was calculated to be 9.55±0.35 and.46±0.32, respectively, in the NVD and ECS groups (P=0.879) (Table 2).

4 Discussion

In the present study, evaluating β-EP concentration suggested that NVD increased the level of β-EP more than ECS, during comparative labor. According to Romano and Lothian, the stages of labor and parturition can be regarded as extreme physical stressors [14]. Furthermore, β-EP and stress hormones are simultaneously released from the anterior pituitary gland into the blood in response to various stressors or pain triggers in humans and mammals [22]. Moreover, β-EP is commonly known as the "nature's narcotic", as it acts on the same receptors as exogenous narcotics. Therefore, as labor progresses, a physiological mechanism modulates the laboring woman's experience of pain and reduces the surge of stress hormones towards the end of labor; it can also facilitate placental expulsion in the second stage [14].

Stress response and inflammation are associated with the secretion of high levels of opioid peptides into the systemic circulation [23]. Natural stress, induced by exercise and labor, is associated with increased plasma levels of these hormones. Besides, β-EP, as a stress hormone, is functionally similar to cortisol and catecholamine [24]. Previous studies reported no significant difference in the cord plasma levels of β-EP between NVD and ECS women. However, these studies included relatively small sample size, recruited a mixed population, and used an endorphin assay, i.e., not very accurate [25, 26].

The maternal plasma β-EP concentration slowly increases during different stages of labor and cervical dilation. This increase is attributed to the enhanced secretion of ACTH and β-EP during labor and delivery [14]. Hormones, such as estrogen, progesterone, β-EP, human chorionic gonadotropin, and cortisol, increase during pregnancy and significantly drop after birth [23]. Perinatal stress, like NVD, can alter the endocrine markers of stress response to painful stimuli, i.e., detectable months after delivery [19].

We found that the umbilical cord plasma levels of β-EP were higher in the NVD group, compared to the ECS group. These findings were similar to those of Vogl et al., probably due to the lower stress level in the latter group [24]. Overall, the plasma level of β-EP is a measure of stress not only in the mother but also in the fetus [27]. Another study found that β-EP release in response to exercise was enhanced in pregnancy [28]; therefore, regular exercise during pregnancy may elevate the level of β-EP in pregnancy and labor and decline the need for analgesics [22].

Previous studies reported comparable levels of β-EP in infants born vaginally without analgesia and those born via ECS [29, 30]. These discrepancies may be attributed to the selection of samples, sample size, and the classification of samples. In addition, differences in absolute β-EP concentrations may be largely related to variations in measurement methods and antibody specificity. However, studies signified lower levels of β-EP and stress hormones, like cortisol, in ECS newborns, compared to infants born vaginally [31, 32]. Overall, researchers have concluded that ECS is less stressful for the newborn.

The majority of previous studies confirm that maternal plasma levels of β-EP increase during labor, reaching the

maximum level during NVD [16]. Endogenous opioid peptides, including β-EP and catecholamine, were implicated for modulating pain and stress. The pituitary gland releases these hormones in response to stress. Since β-EP has a short half-life (37 minutes), a full-term fetus can probably produce endorphins from the pituitary gland [22]. Therefore, an enhanced β-EP level may help the fetus endure distress during delivery. It can be also important for neonatal development during and after the perinatal period [14] or even months after delivery [33].

Corticosteroids, released in response to stress, are used for pulmonary maturation; they increase the surfactant synthesis required for lung maturation. Endorphins released during delivery elevate the prolactin release, which contributes to active pulmonary maturation. The level of β-EP, as a natural opioid peptide, increases under a wide range of stressful conditions [16]. Our findings revealed that NVD may increase the level of β-EP during delivery. It is hoped that our findings help health administrators and researchers take effective measures towards reducing ECS rates and improving the future of child health indicators in society.

5. Conclusion

Pregnancy and childbirth is a completely physiological and natural phenomenon that requires support and leadership before management and intervention. Considering the documentation on the complications of cesarean delivery for mother and infant, as well as the benefits of natural delivery, it is necessary to use physiological methods based on evidence and appropriate methods for managing a low-risk pregnancy and safe pregnancy control and reducing the extent of elective cesarean section.

Future studies are recommended to examine β-EP levels every 3 months during pregnancy and after delivery. In addition, using larger sample size, hormone assessment in different pain reduction methods, and the efficacy assessment of these methods in β-EP secretion are suggested.

Because of the limited sampling due to the specific number and standard of the beta-endorphin test kit, the study was conducted n a limited sample. It is suggested that future studies use large sample sizes and compare beta-endorphin levels during pregnancy and postpartum.

The hormonal physiology of childbirth has evolved to optimize reproductive success. Early prenatal exposure to stress or stress during delivery can change the hypothalamic-pituitary-adrenal axis and influence fetal development. β-EP facilitates maternal adaptation and may promote mother-infant attachment by priming maternal reward centers at birth. The corelease of oxytocin with β-EP during breastfeeding and maternal-infant contact may maintain maternal attachment, with benefits for neonatal survival. This research was conducted for the first time in Iran. Similar and controversial studies were conducted in different countries; therefore, reports from Iran were compared with those of other countries. Considering racial, cultural, and social variations in Iran, NVD has greater effects on the release of β-EP in comparison with ECS.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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This study was extracted from a MA. thesis of second authors at the Department of Midwifery, School of Nursing and Midwifery, Isfahan University of Medical Sciences, Isfahan, Iran.

Authors' contributions

Conceptualization and supervision: Shahnaz Tork-Zahrani, Farahnaz Heshmat, Hanieh Abbasinia, Hossein Delshad, Nezhat Shakeri; Methodology: Hossein Delshad, Nezhat Shakeri; Investigation, writing – original draft, and writing – review & editing: All authors; Data collection: Farahnaz Heshmat, Hanieh Abbasinia, and Mahboobeh Valiani; Data analysis: Farahnaz Heshmat and Nezhat Shakeri.

Conflict of interest

The authors declared no conflicts of interest.

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