Reprinted from AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, St. Louis
Vol. 152, No. 1, PP. 56-59, May 1, 1985 (Printed in the U. S. A.)


# Maternal and fetal β-endorphin release in response to the stress of labor and delivery

**George D. Kofinas, M.D., Alexander D. Kofinas, M.D., and Farangis M. Tavakoli, M.D.**
*Brooklyn, New York*

In order to clarify the stress effect of labor on maternal and neonatal plasma levels of β-endorphin, we measured this peptide in samples taken from 40 pregnant patients and their neonates at the time of normal vaginal delivery (n = 15), and at cesarean section performed either in early labor (n = 13) or prior to labor (n = 12). The mean (± SE) maternal plasma concentration of β-endorphin in the vaginal delivery group was 40.3 ± 5.6 fmol/ml, which was significantly higher than that in their neonates (21.3 ± 2.9 fmol/ml). In contrast, maternal levels of β-endorphin in the cesarean section groups (8.2 ± 1.2 and 8.5 ± fmol/ml) were significantly lower than those in their neonates (23.3 ± 5.6 and 15.6 ± 2.8 fmol/ml). Concentrations of β-endorphin in mothers delivered vaginally were also significantly higher than those in mothers delivered by cesarean section. However, there was no difference in mean cord levels of β-endorphin among the three groups. These findings indicate that (1) neither the presence or absence of labor affects fetal plasma β-endorphin secretion and (2) the stress of labor and delivery produces a marked increase in maternal release of β-endorphin. (Am J Obstet Gynecol 1985;152:56-9.)

**Key words:** β-Endorphin, labor, stress

*From the Department of Obstetrics and Gynecology, The Brooklyn Hospital–Caledonian Hospital.*
*Presented at a meeting of the Brooklyn Gynecological Society, Brooklyn, New York, April 18, 1984.*
*Received for publication July 9, 1984; revised October 11, 1984; accepted November 1, 1984.*
*Reprint requests: Dr. George D. Kofinas, Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, SUNY Downstate Medical Center, 450 Clarkson Ave., Box 24, Brooklyn, NY 11203.*

β-Endorphin is a 31-residue opioid peptide formed by enzymatic cleavage of β-lipotropin, a split product from pro-opiomelanocortin, which is also the precursor of adrenocorticotropin (ACTH).[1] All of the above-mentioned peptides are localized within the pituitary corticotrophs,[2] and the adenohypophysis is the major source of endorphins, particularly β-endorphin, that are found in peripheral blood during stress.[3] Guillemin

et al.[3] reported that in rats ACTH and β-endorphin are concomitantly secreted by the pituitary gland in response to acute stress, and hypophysectomy abolishes this response.

Since labor and delivery are considered to be states of extreme emotional and physical stress, the pro-opio melanocortin derivatives may be involved in the mechanisms of maternal and fetal adaptation to this stressful state. Csontos et al.[5] have already shown that maternal plasma levels of ACTH and β-endorphin are markedly elevated during labor, with the highest concentrations immediately after delivery. They also found high umbilical cord plasma levels of β-endorphin, but lower than maternal levels. No data have been published on the fetal plasma levels of β-endorphin in early labor. In an attempt to clarify further the role of β-endorphin, we measured this opioid in maternal and umbilical cord plasma at the time of vaginal delivery and at cesarean section in patients either in early labor or prior to labor.

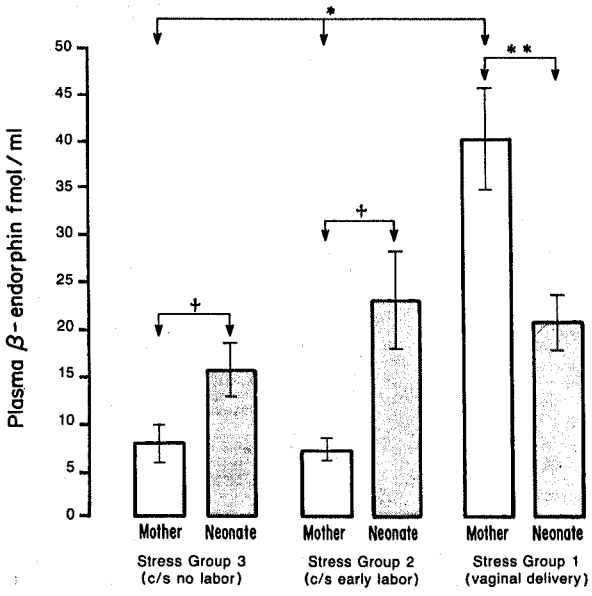


**Fig. 1.** Mean (±SE) concentrations of β-endorphin in maternal and neonatal plasma in the three different stress groups. (*$p < 0.001$; **$p < 0.01$; †$p < 0.05$). *c/s* = Cesarean section.

## Material and methods

The study involved 40 pregnant patients and their neonates, divided into three "stress" groups. Stress group 1 consisted of 15 mothers and their neonates who had an uneventful labor and normal vaginal delivery. Stress group 2 consisted of 13 mothers and their neonates who were delivered by cesarean section when they were in definite early labor (cervical dilatation <5 cm). The indications for their surgical delivery were previous cesarean section (n = 11) and high breech presentation in labor (n = 2). Stress group 3 consisted of 12 mothers and their neonates who were delivered by elective repeat (n = 9) or primary (n = 3) cesarean section in the absence of labor. All mothers in the three groups were healthy and had normal antepartum courses, except for two who had Class B diabetes and one who was chronically hypertensive in group 3. All of them were delivered between 35 and 41 weeks' gestation. None of the 40 mothers received any medication, including analgesics, prior to delivery or induction of anesthesia. Eight mothers from group 2 and eight from group 3 were delivered under general anesthesia, and the rest under epidural anesthesia.

All neonates in the three groups had 1-minute Apgar scores >7, except for two delivered by cesarean section (groups 2 and 3), who had scores of 6 and 8 and 6 and 9, respectively.

Blood was withdrawn from the mothers in 10 ml plastic syringes at 1 minute before the induction of anesthesia or at the time of vaginal delivery. Mixed umbilical cord blood (5 ml) was collected within 1 minute after the cord was clamped and cut. All collected samples of blood were placed into ice-chilled siliconized glass tubes that contained ethylenediaminetetraacetic acid and bacitracin. The specimens were centrifuged immediately thereafter for 30 minutes at 3,000 rpm at 4° C, and the supernatant plasma was transferred into chilled siliconized glass tubes, immediately frozen, and stored at −75° C until assayed.

β-Endorphin was extracted from plasma by affinity gel extraction method with the use of specific Sepharose adsorption particles and then measured by a highly specific radioimmunoassay (β-endorphin radioimmunoassay kit, Immunonuclear Corp., Stillwater, Minnesota). This radioimmunoassay method is based on a rabbit antibody with high sensitivity to β-endorphin. The antibody to β-endorphin cross-reacts 100% with human β-endorphin, (Des-Tyr') human β-endorphin, (2-me-Ala[2]) β-endorphin, and N-acetyl β-endorphin. The antibody demonstrated 5% cross-reactivity with β-lipotropin (β-LPH), and no cross-reactivity with α-endorphin (β-$LPH^{61-76}$), γ-endorphin (β-$LPH^{61-77}$) (D-Ala[2])- β- endorphin, dynorphin, α-neo-endorphin, leukine enkephalin, methionine enkephalin, $ACTH^{1-39}$, $ACTH^{1-24}$, α-melanocyte–stimulating hormone, prolactin, follicle-stimulating hormone, luteinizing hormone, thyrotropin, vasopressin, and oxytocin.

Assays were performed in duplicate, and the results were averaged. The intra-assay and interassay coefficients of variation were 13.7% and 18.1%, respectively. Results were evaluated by analysis of variance and two-tailed Student's *t* test and corroborated by nonparametric procedures.

## Results

The maternal and cord plasma concentrations of β-endorphin at the time of delivery in the three stress groups are shown in Fig. 1.

The mean ± SE plasma β-endorphin concentration measured at the time of delivery in 15 mothers delivered vaginally (stress group 1) was 40.3 ± 5.6 fmol/ml, which was significantly higher ($p < 0.01$) than the mean plasma β-endorphin concentration (21.3 ± 2.9 fmol/ml) of their neonates. In contrast, the mean plasma concentrations of β-endorphin in mothers delivered by cesarean section in early labor (stress group 2: 8.2 ± 1.2 fmol/ml), as well as those not in labor (stress group 3: 8.5 ± 1.9 fmol/ml) were significantly lower ($p < 0.05$) than those of their neonates (23.3 ± 5.6 and 15.6 ± 2.8 fmol/ml, respectively).

Comparison among mean maternal plasma levels of β-endorphin indicates that mothers delivered vaginally have values significantly higher ($p < 0.001$) than those of mothers delivered by cesarean section, whether in early labor or not. However, there was no difference in mean cord plasma concentrations of β-endorphin among the three groups.

## Comment

This study was designed to assess maternal and umbilical cord plasma levels of β-endorphin in response to gradually increasing levels of stress (no labor, early labor, and full labor) and the possible relationship of maternal plasma concentration of β-endorphin to umbilical cord plasma level of β-endorphin. Our data indicate that there is no significant difference in the mean levels of umbilical cord plasma β-endorphin among the three stress groups. Also, there was no difference in the mean levels of β-endorphin in the maternal plasma during early labor (stress group 2) as compared to the state of no labor (stress group 3). However, there was a significant fivefold increase in the maternal plasma levels of β-endorphin after full labor (stress group 1).

A comparison of maternal and cord mean plasma levels of β-endorphin in each stress group separately revealed that in the no-labor and early labor groups the mean cord plasma levels of β-endorphin were significantly higher than the corresponding maternal levels. This relationship was reversed in stress group 1 (vaginal delivery), in which we observed maternal levels significantly higher than the corresponding cord plasma levels of β-endorphin.

Our results are in agreement with, and extend the findings of Csontos et al.,[5] who reported that maternal plasma β-endorphin at the time of vaginal delivery is significantly higher than the cord plasma levels of β-endorphin. Other investigators[4-7] did not find a difference between maternal and cord plasma levels of β-endorphin. However, those studies included a relatively small number of subjects, used a mixed population, and/or used an endorphin assay that was not very specific.

Interestingly, Wardlaw et al.[8] reported an inverse correlation between umbilical cord plasma levels of β-endorphin and pH and $Po_2$, thus suggesting that the increased levels of β-endorphin were the result of fetal hypoxia and acidosis. Shaaban et al.[9] found significantly higher levels of β-endorphin in neonates with fetal distress, thus supporting the findings of Wardlaw et al. that fetal hypoxia elevates the levels of β-endorphin in cord plasma. Our finding that neither the presence or absence of labor nor the method of delivery affects fetal plasma levels of β-endorphin in the absence of fetal distress is in agreement with these findings.

The lack of correlation between the simultaneously measured maternal and cord plasma levels of β-endorphin in all three stress groups suggests that the maternal and fetal secretions of β-endorphin are independently regulated. It is well known that β-endorphin is secreted in response to acute stresses, such as pain and insulin-induced hypoglycemia, as well as administration of Pitressin and metyrapone. The increased circulating amounts of β-endorphin after stress are hypophyseal in origin.[3] The high concentrations of β-endorphin in maternal plasma at the time of delivery probably provide some degree of analgesia to the mother. They may also counteract the effects of the high levels of catecholamines on the cardiovascular system. The physiologic role and significance of β-endorphin present in the fetal circulation remains totally unknown. The finding that the stress of labor and delivery does not affect the fetal β-endorphin system tempts us to speculate that either pain is not a stimulus for the release of β-endorphin in the fetus, or the fetus does not suffer pain during labor.

We are indebted to Dr. F. I. Reyes for his instructive remarks and critique during the preparation of the final manuscript.

## REFERENCES

1. Mains RE, Eipper BA, Ling N. Common precursor to corticotropins and endorphins. Proc Natl Acad Sci USA 1977;74:3014.
2. Bloom F, Battenberg E, Rossier J, Ling N, Lepaluoto J, Vargo TM, Guillemin R. Endorphins are located in the intermediate and anterior lobes of the pituitary gland, not in the neurohypophysis. Life Sci 1977;20:43.
3. Guillemin R, Vargo T, Rossier J, Minick S, Ling N, Rivier C, Valle W, Bloom F. β-Endorphin and adrenocorticotropin are secreted concomitantly by the pituitary gland. Science 1977;197:1367.
4. Wilkes MM, Stewart RD, Bruni JF, Quigley ME, Yen SSC, Ling N, Chretien N. A specific homologous radioimmunoassay for human β-endorphin: direct measurement in biological fluids. J Clin Endocrinol Metab 1980;50:309.
5. Csontos K, Rust M, Hollt V, Mahr W, Kromer W, Teschemacher HF. Elevated plasma β-endorphin levels in pregnant women and their neonates. Life Sci 1979;25:835.

6. Genazzani AR, Facchinetti F, Parrini D. β-Lipotropin and β-endorphin plasma levels during pregnancy. Clin Endocrinol 1981;14:409.
7. Kimball CD, Chang CM, Huang SM, Houck JC. Immunoreactive endorphin peptides and prolactin in umbilical vein and maternal blood. AM J OBSTET GYNECOL 1981;140:157.
8. Wardlaw SL, Stark RI, Baxi L, Franz AG. Plasma β-endorphin and β-lipotropin in the human fetus at delivery: correlation with arterial pH and $P_{O_2}$. J Clin Endocrinol Metab 1979;49:888.
9. Shaaban MM, Hung TT, Hoffman DI, Lobo RA, Goebelsmann U. β-Endorphin and β-lipotropin concentrations in umbilical cord blood. AM J OBSTET GYNECOL 1982;144:560.