Amniotic Fluid β-Endorphin Levels and Labor

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To define the relationship between amniotic fluid concentrations of β-endorphin immunoreactivity and onset of parturition, we measured this opioid in samples obtained during cesarean section at term. A total of 27 women were studied, 14 without labor and 13 in early labor. Mean (± SE) amniotic fluid β-endorphin levels were significantly lower in patients in labor than in those not in labor (3.2 ± 0.05 versus 8.4 ± 1.0 fmol/mL). The mean β-endorphin level (21.1 ± 4.2 fmol/mL) in other amniotic fluid samples obtained during the second trimester of pregnancy was significantly higher than mean values at term. These differences in amniotic fluid β-endorphin levels may support the theory of an opioid mechanism involved in parturition. *(Obstet Gynecol 69:945, 1987)*

Beta-endorphin is an opioid peptide derived by the selective proteolytic cleavage from β-lipotropin of the 91 amino-acid carboxyterminal fragment of pro-opiomelanocortin.[1] This opioid, like its precursor pro-opiomelanocortin, is produced by different organs such as the brain, pituitary gland, and placenta.[2] Furthermore, β-endorphin is found in circulating fluids, including amniotic fluid and fetal blood.[2] Although changes of cord blood and amniotic fluid β-endorphin concentrations have been associated with fetal maturity and well-being,[3–5] the physiologic role of this opioid in amniotic fluid remains unclear.

Morphine and other opioids influence smooth muscle contractility.[6,7] Because amniotic fluid β-endorphin levels appear to decrease with advancing gestation,[4] it is possible that an opioid mechanism may be involved in the maintenance of pregnancy and the onset of parturition. In order to clarify this question, we studied amniotic fluid β-endorphin immunoreactivity levels just before and shortly after onset of spontaneous labor.

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Materials and Methods

The study involved 27 pregnant women at term gestation, divided according to the presence of labor. One group consisted of 14 women who were delivered by elective repeat ($N = 11$) or primary ($N = 3$) cesarean section without labor. The other group consisted of 13 women also delivered by cesarean section, during early spontaneous labor with 2–5 cm cervical dilatation. The indications for abdominal delivery in this group were previous cesarean section in 11 women and breech presentation in the other two. The nonlabor group included two class B diabetics and one woman with chronic mild hypertension. All laboring patients were healthy. The amniotic membrane was intact in all cases. None of the women received any medication, including narcotic analgesics, before anesthesia. Epidural anesthesia was used in four nonlabor and in five labor patients; the rest received general anesthesia of the same type. For comparison, we collected additional amniotic fluid samples from 12 normal women who underwent diagnostic amniocentesis at 16–20 weeks' gestation.

Amniotic fluid samples obtained by direct amniocentesis during cesarean section were collected in ice-chilled siliconized glass tubes containing ethylene diamine tetra-acetic acid (EDTA) and bacitracin. The specimens were centrifuged immediately at 3000 rpm at 4C for 30 minutes; the supernatant was then stored at −75C until assayed. As others[8] have shown, collection of samples in chilled siliconized glass tubes with an anticoagulant and a protease inhibitor prevents degradation of endorphins. The concentration of β-endorphin does not vary significantly, even after several thawing steps, when samples obtained under these conditions are kept at low temperatures.

Beta-endorphin was extracted from the amniotic fluid by an affinity gel extraction method using sepharose adsorption particles, and then measured by radioimmunoassay (β-endorphin RIA Kit, Immunonuclear Corp., Stillwater, MN). The antibody to

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endorphin cross-reacts 100% with human β-endorphin, (Des-Tyr[1]) 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$^{61-77}$) dynorphin, (D-Ala[2]) β-endorphin, α-neoendorphin, leukine enkephaline, methionine enkephaline, adrenocorticotropic hormone (ACTH)$^{1-39}$, ACTH$^{1-24}$, α-melanocyte-stimulating hormone (MSH), prolactin (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), vasopressin, and oxytocin. Assays were performed in duplicate and the results were averaged. The intra-assay and interassay coefficients of variation of this radioimmunoassay were 13.7 and 18.1%, respectively. The data were evaluated statistically by Student's *t* test.

Results

The two groups were similar with respect to maternal age (mean ± standard error [SE]: 28.8 ± 2.1 versus 26.8 ± 1.6 years), gestational age (38.4 ± 0.4 versus 38.7 ± 0.4 weeks), and birth weight (3215 ± 236 versus 3215 ± 185 g). Because amniotic fluid β-endorphin levels in the hypertensive and diabetic patients were similar to those from healthy patients, they were included for statistical analysis. In addition, the β-endorphin concentrations in samples from patients who received epidural anesthesia were not significantly different from those given general anesthesia within groups. Thus, these results were also pooled.

Amniotic fluid β-endorphin concentrations in patients without labor (8.4 ± 1 fmol/mL) were significantly higher ($P < .05$) than those obtained during early labor (3.2 ± 0.05 fmol/mL). The mean amniotic fluid level found in samples obtained during the first half of pregnancy (21.1 ± 4.2 fmol/mL) was significantly higher than mean values found at term ($P < .01$).

Discussion

We found that, at term gestation, amniotic fluid β-endorphin levels were lower in women in early labor than in women not in labor. We also found, as have others,[4] that second-trimester concentrations of β-endorphin in amniotic fluid are higher than at term.

The origin of amniotic fluid β-endorphin, like its physiologic role, is far from clear. There are at least four potential sources: maternal and fetal circulations, placenta, and decidua. A maternal origin is doubtful, considering that placental transfer of other peptide hormones such as ACTH is essentially nil.[9] Decidual cells are capable of protein hormone synthesis, but it is unknown whether they produce β-endorphin or its precursors. On the other hand, it has been shown that trophoblastic tissue produces β-endorphin,[10] and this hormone has been found in the fetal circulation.[3,11] Thus, the most likely sources of amniotic fluid β-endorphin are the placenta and the fetal pituitary gland, but a decidual origin cannot be excluded. Fetal plasma β-endorphin levels do not change with labor at term gestation, as we found previously[11] in mixed cord blood samples obtained from the same patients, and also do not change at the same time as the amniotic fluid samples reported herein. Therefore, decreased production by the fetal pituitary could not explain the fall in amniotic fluid levels during labor, which may instead result either from decreased production by the placenta or perhaps the decidua, or from increased removal by fetal swallowing or enzymatic destruction. The apparent decrease in amniotic fluid β-endorphin levels with advancing gestation could be the result of not only inflow and outflow changes, but also of a simple dilutional effect from the normal rise of amniotic fluid volume throughout pregnancy. The apparent further decline in amniotic fluid β-endorphin levels associated with early labor may result also from decreased opioid production or changes in fluid volume. Simultaneous measurement of other amniotic fluid constituents (eg total protein) might help to clarify this issue.

A decline in amniotic fluid concentration with advancing gestation, and a fall associated with labor, agrees with the notion that an opioid mechanism may be related to the unfolding of uterine activity leading to parturition. High local β-endorphin concentrations during the first half of gestation would promote uterine relaxation, whereas lower levels at term before and during labor would favor uterine contractility. Clinical studies on the effect of morphine and meperidine during spontaneous or induced labor report variable results most probably due to methodological pitfalls.[12–14] Experimental studies indicate that β-endorphin and other opioids exert a direct effect upon smooth muscle.[15] In vitro studies, however, demonstrate definite antagonism by opioids on the prostaglandin E_2 and oxytocin-induced uterine contractility.[6,7] It is plausible that opioids' myometrial effect may vary according to gestational age, as well as the presence or absence of well established labor.

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