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Third Trimester POMC Disregulation Predicts Use of Anesthesia at Vaginal Delivery

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SANDMAN, C. A., P. D. WADHWA, A. CHICZ-DEMET, M. PORTO AND T. J. GARITE. *Third trimester POMC disregulation predicts use of anesthesia at vaginal delivery.* PEPTIDES **16**(2) 187–190, 1995.—In a prospective study, third trimester plasma levels of BE and ACTH were determined in 58 women who delivered vaginally. Peptide regulation was compared between subjects who used conduction anesthesia at delivery and subjects who did not. Third trimester levels of maternal BE and ACTH were significantly related; however, the relationship was significant only in subjects who did not receive conduction anesthesia (n = 24) at delivery. The normal corelease pattern between BE and ACTH in subjects receiving conduction anesthesia (n = 34) during birth was uncoupled. The use of conduction analgesia during vaginal delivery was significantly related to a disregulation index created to quantify the BE-ACTH release pattern. Uncoupled ACTH and BE patterns may result from modified control of proopiomelanocortin (POMC) expression during pregnancy or unique proteolytic processing of POMC, and may alter pain tolerance during delivery.

ACTH β-Endorphin (BE) Third trimester Opiates Proopiomelanocortin (POMC) Conduction anesthesia

THE significant elevation in plasma of maternal β-endorphin (BE) at delivery may reflect the stress of birth and may possibly reduce the pain associated with child birth (7,16,29). The significance of elevated levels of coreleased peptides BE and adrenocorticotrophic hormone (ACTH) in maternal plasma and in amniotic fluid between conception and the third trimester of pregnancy is unknown (3,10,11,14,22,32). It is possible that patterns of peptide release during the third trimester prepare the mother for the pain and stress of delivery. The purpose of the present investigation was to determine whether third trimester opiate levels or disruption of coreleased proopiomelanocortin (POMC) products, BE and ACTH, predicted the use of conduction anesthesia during vaginal delivery.

METHOD

Subjects

Fifty-eight subjects (from an initial sample of 76) who delivered vaginally constituted the study sample. All subjects giving consent were English-speaking adults with a singleton intrauterine pregnancy. Subjects were not excluded based on obstetric risk. Subjects were approached consecutively for participation during the late second trimester of their pregnancy. Informed consent was obtained according to the procedures of the University of California.

Procedures

Blood samples (20 ml/draw) were withdrawn at 27–29 weeks of gestation by antecubital venipuncture into siliconized EDTA (purple top) vacutainers and placed on ice immediately. All samples were centrifuged at 2000 × g (10 min) within 15 min (average was less than 10 min) and the plasma was decanted into polypropylene tubes containing 500 KIU/ml aprotinin (Sigma Chemical Company, St. Louis, MO). The samples were stored at −70°C until assayed.

Neuropeptide Measures

β-Endorphin assay. Plasma levels of β-endorphin (BE) were determined by a commercially available solid-phase two-site immunoradiometric assay (IRMA; Nichols Institute Diagnostics, San Juan Capistrano, CA). The antiserum has 1.6% cross-reactivity with β-lipotropin at 500 pg/ml and has < 0.01% cross-reactivity with related opiates at 5 μg/ml. Samples were assayed in duplicate (200 μl per assay tube). [^{125}I]Anti-BE (rabbit) solution (100 μl) was added to each tube and vortexed. The reaction was initiated by adding one anti-BE (rabbit)-coated polystyrene bead to the assay tube followed by a stationary incubation at room temperature for 20 ± 4 h. The beads were then washed twice with phosphate-buffered saline and aspirated to dryness. The labeled antibody complex bound to the solid phase was measured using a Micromedic Isoflex Gamma Counter. The Allegro Beta-Endorphin Immunoassay system has a minimum detectable dose (MDD) of 10 pg/ml (95% confidence limit) with a coefficient of variance (CV) of 4.1% (intra-assay) and 9.0% (inter-assay) at the highest concentrations expected in the present study.

ACTH assay. Plasma levels of ACTH were measured by a commercially available radioimmunoassay (Nichols Institute Di-

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agnostics). The antiserum employed has < 0.001% cross-reactivity with BE and ACTH fragments. Samples were assayed in duplicate (200 μl per assay tube). ACTH [^{125}I]antibody solution (100 μl) was added to the samples, vortexed, and incubated at room temperature for 20 ± 2 h after the addition of an avidin-coated bead. The solid matrix was washed with buffered surfactant in phosphate-buffered saline to remove unbound components, and the bound radiolabeled antibody complex was quantified using a Micromedic Isoflex Gamma Counter. The ACTH assay has a MDD of 1.0 pg/ml (95% confidence) with CV of 3.0% (intra-assay) at 35 pg/ml and 7.8% (inter-assay) at 36 pg/ml.

Data reduction for the RIA assays were done by a computer assisted four-parameter logistics program by DeLean, Munson, and Rodbard (9).

Use of Conduction Anesthesia

Maternal medical and obstetric history, prenatal care (gestational age at first prenatal visit, total number of prenatal visits), antepartum risk, labor and delivery parameters, and birth outcome were obtained from medical charts (30). Maternal labor and delivery parameters included mode of delivery and the use of anesthesia during delivery. For the purpose of the present analysis, only subjects with vaginal delivery were included. Use of conduction anesthesia was recorded if the subject received epidural anesthetic (general anesthesia was used with one subject).

RESULTS

Third trimester levels of maternal BE and ACTH were significantly ($r = 0.48, p < 0.001$) related [Fig. 1(A)]. As presented in Fig. 1(B), however, the significant relationship between third trimester BE and ACTH was apparent only in women ($n = 24$) who did not receive conduction anesthesia at delivery ($r = 0.81$, $p < 0.001$). The usual corelease relationship between BE and ACTH was uncoupled during the third trimester in women who received conduction anesthesia ($n = 34$) at delivery, as reflected by the low correlation ($r = 0.28, p$ = NS) and variable scatter in Fig. 1(B).

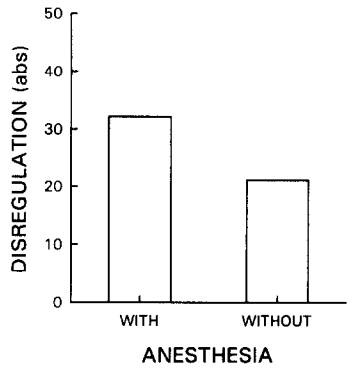

FIG. 2. Women who received conduction anesthesia at delivery had a significantly higher disregulation index during the third trimester than women delivering without anesthesia.

A disregulation index (DI) was created to quantify the βE/ACTH corelease pattern by the equation: DI = [(BE-ACTH)/BE) × 100. A high DI indicated that the plasma BE is higher than ACTH. Index values close to zero indicated no difference in levels of BE and ACTH, and negative scores reflect higher ACTH concentrations relative to BE.

The use of analgesia during vaginal delivery was significantly related to larger absolute values (magnitude) of the DI, $F(1, 56) = 4.76, p < 0.03$. Subjects receiving conduction anesthesia during vaginal delivery had third trimester DI values of 32.56 ± 19.6 compared with DI values of 22.04 ± 16.5 among subjects who delivered without conduction anesthesia (Fig. 2). Although the disregulation indicated that BE was higher in subjects with

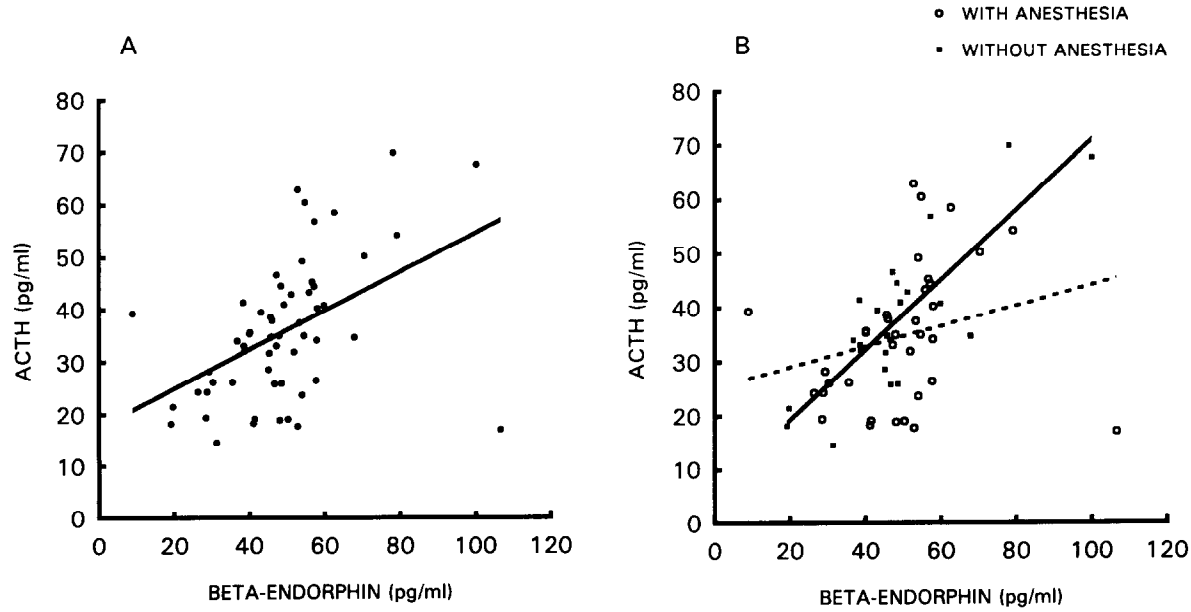

FIG. 1. (A) Highly significant ($r = 0.48, p < 0.001$) scatterplot of the relationship between BE and ACTH in pregnant women ($n = 58$) during the third trimester. (B) Scatterplot of the relationship between BE and ACTH during the third trimester separated into women delivering vaginally, who received conduction anesthesia ($n = 34$, solid dots and line) and women who did not receive conduction anesthesia ($n = 24$). The relationship between BE and ACTH was only significant among women who did not receive conduction anesthesia at delivery.

TABLE 1

DEMOGRAPHIC CHARACTERISTICS OF THE STUDY SAMPLE

Age (years)	30.15 ± 5.96 y
Range (years)	18–45 y
Parity	
Primiparous	31%
Multiparous	69%
Education	
High school graduates	44%
College graduates	56%
Marital status	
Married	83.7%
Separated/divorced	10.2%
Single	6.1%
Ethnicity	
Anglo	77.6%
Hispanic	24.4%
Annual family income	
<$20,000	22.4%
$20,000–39,000	18.3%
$40,000–49,999	18.4%
>$50,000	40.8%

conduction anesthesia (25.63 ± 28.28 vs. 17 ± 21.8), this effect was not statistically significant, $F(1, 56) = 1.61$, $p = 0.21$).

DISCUSSION

Growing evidence implicates BE and ACTH levels at birth as a marker of perinatal complications (8,10,13,15,18,27,31). Elevation of BE at birth may provide analgesic relief from the pain of vaginal delivery (7,16,29). Findings from this study suggest that disregulation or uncoupling of the relationship between BE and ACTH during the third trimester prospectively predicted maternal utilization of conduction anesthesia during vaginal delivery. Subjects with normal corelease patterns did not receive anesthesia during birth. It is conceivable that changes in the release pattern of ACTH and BE during the third trimester in some women may alter peptide receptor sensitivity. If opiate receptors are altered by these release patterns during the third trimester, the elevation of BE at term may not be effective in modulating the experience of pain of vaginal delivery, requiring the use of anesthesia in these women.

BE and ACTH are systemically coreleased from the adenohypophysis in healthy adults in response to pain, physical stress (17,26), and psychological stress (19,20,23). The precise mechanism responsible for the regulation of peptides in the third trimester of pregnancy is not known, but it most probably involves hypothalamic control of adenohypophyseal function (21). The placenta acquires endocrine properties (28); however, it probably does not contribute to the disregulation observed among women requiring conduction anesthesia at birth. For instance, although the placenta releases CRF into maternal blood, it is bound and biologically inactive as a source of pituitary stimulation of BE and ACTH (4,33). The placenta also releases BE (5,6), but it is *N*-acetylated (1,35) and may not be detected by our assay. Uncoupling of BE and ACTH may be related to differential proteolytic processing of POMC. There is disagreement whether ACTH and BE are translated from the POMC molecule by different (2) or identical (25) enzymes. The intriguing possibility (2) that ACTH and BE are cleaved by different enzymes provides a mechanism to explain the current findings. The pattern of disregulation observed in this study could result from either decreased activity of the enzyme mPC1 (less ACTH) or increased activity of the enzyme mPC2 (relatively more BE). Because enzyme activity is controlled by genetic and environmental factors (12), the differential regulation of PC1 and PC2 could account for the release patterns observed in this study.

It is possible that third trimester disregulation of BE-ACTH release results from activity of PC1 and PC2 enzymes triggered by environmental factors such as stress (12). Uncoupling of BE and ACTH in women who use conduction anesthesia at birth may be a marker of conditions such as anxiety and stress known to relate to increased pain at birth (24,34). Consequently, determining the pattern of BE and ACTH during the third trimester may provide important information about risk during birth and suggest strategies for the management, care, and pain relief of women at delivery.

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