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ORIGINAL ARTICLE

Maternal and fetal hypothalamo-pituitary-adrenal axis: different response depends upon the mode of parturition

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Abstract

OBJECTIVES: The changes in corticotropin releasing hormone (CRH), adrenocorticotropin hormone (ACTH), cortisol and dehydroepiandrosterone (DHEA) in maternal and fetal plasma were estimated in two group of women undergoing labour after oxytocin induction, or elective cesarean section to correlate changes in maternal and fetal HPA axis to the different stressor conditions. **MATERIALS AND METHODS:** Blood was sampled from a maternal peripheral vein two days before labour, during the second stage of labour and on the second postnatal day, and also from umbilical vessels just after delivery. Hormone concentrations were measured by RIA and ELSA methods. The maternal plasma CRH concentration before and after labour was similar in both studied groups. **RESULTS:** Plasma CRH levels measured before labour in both groups were similar, but during labour after oxytocin infusion declined, and was in group of women with elective cesarean section rose, after the delivery there was no difference between groups. The plasma ACTH prior to the delivery was at the same level in all subjects, during the third stage of labour ACTH rose in the both groups, but was statistically higher in group with oxytocin infusion. The concentrations of cortisol before delivery was similar in both groups, then rose to the same level during the delivery and then declined to the level observed before delivery. The DHEA concentration was similar in both groups, did not change during the labour, there was no difference between its level in the umbilical vein and artery. In the group with oxytocin-induction there was no correlation between maternal CRH and ACTH or cortisol concentration, but such a correlation occurred in the group with elective cesarean section. The concentration of ACTH and DHEA in umbilical artery was similar in both groups but the concentrations of CRH and cortisol in umbilical artery in group of newborns delivered after elective cesarean section were statistically higher. **CONCLUSION:** The activity of the mother's HPA axis is partially inhibited rather by psychological stressors, than events connected with mode of parturition. The newborn's HPA axis responds in a specific way to mother's HPA-axis. The communication between mother's and newborn's HPA is possibly related to many other factors than placental CRH and ACTH. It is necessary to consider effects of central CRH and ACTH on the fine-tune regulation of HPA axis in the late pregnancy and parturition, not detectable due to the high levels of placental hormones.

Abbreviations
CRH – corticotropin release factor
ACTH – adrenocorticotropin
DHEA – dehydroepiandrosterone
OT – oxytocin
HPA axis – hypothalamo-pituitary-adrenal axis
AVP – arginin-vasopressin

Introduction

The hypothalamic neuropeptide corticotropin-releasing hormone (CRH) is released in response to stress and is a key regulator of pituitary-adrenal function [1]. In vitro studies have shown that CRH and oxytocin are synergistic in enhancing uterine contractility [2]. In humans with advancing pregnancy, placenta and fetal membranes are additional sites of CRH synthesis [2,3]. A specific functional adaptation of the hypothalamo-adrenal-pituitary axis (HPA) during pregnancy and in the peripartum period is a well-known phenomenon [4,5]. It is known that normal development of the HPA axis is important for regulation of intrauterine homeostasis, maturation of vital organ systems, and may influence the timing of parturition [6,7]. The regulation of the hormonal response to stress during pregnancy, despite its obvious implications for fetal and maternal well-being is not clear yet [5]. Placental CRH, due to its similarity in structure to the peptide from hypothalamic origin, has been postulated to stimulate maternal as well as fetal pituitary ACTH release [8,9]. We [10,11] and others [12] have previously shown that there is no correlation between CRH levels and answer of maternal, as well fetal HPA axis. Despite of elevated levels of CRH, ACTH, as well as cortisol levels remain not elevated, and rather respond to the operative stress during the labour. Additionally, in earlier studies no data seems to be available whether or not labour affect in the same way maternal and fetal HPA axis. Our earlier studies showed that answer of maternal and fetal HPA axis is not positively correlated to the stressor factors, like operative way of ending the labour, cause by hypoxia of fetus [data not published].

In order to examine maternal and fetal HPA axis acting during stress of childbirth, we investigated the changes in concentration in plasma CRH, ACTH, cortisol and DHEA in women undergoing labour induction by oxytocin infusion, or elective cesarian section. In both groups did not occur spontaneous contractions.

Lack of spontaneous contraction and early emotional preparation to the onset of the labour allow to eliminate additional stress factors. The aim of this study was to investigate the relationship between hormones of HPA axis in mother and newborn, in response to obstetric events during labour.

Materials and methods

Subjects and protocol

The study was carried out at the Perinatology Clinic, First Department of Gynecology and Obstetrics, Medical University of Łódz, Poland. The protocol of experiment was accepted by Ethical Committee of Medical University of Łódz. Blood samples were obtained from 35 healthy women at term without uterine contractions 2–4 days before delivery (at 7.00 a.m.), then at the beginning of the third stage of labour, and finally on the second day after delivery (again at 7.00 a.m.). Blood samples were also taken from the umbilical vein and artery immediately after the placenta was born. Following centrifugation plasma was apportioned for different assays. After birth, the weight, length and biochemical conditions of the newborn were checked.

Participants were divided into two groups. The first group of women (16 subjects) gave birth in a way of elective cesarean section. The second group (16 women) underwent induction of labour at term. The method of induction involved oxytocin infusion due to the lack of spontaneous contractions.. The protocol of the induction of labour involved an intravenous oxytocin infusion followed by amniocentesis if regular contractions had begun. The oxytocin infusion was commenced at rate 1 mU/min and increased at 15 min intervals until effective labour was established, to a maximum rate 40 mU/min. The first stage of labour in this group lasted an average of 5 hours.

The gestational age of all the women was 39–42 weeks. The mean of gestational age of both groups was similar (38 ± 5, and 40 ± 2 weeks, respectively). The subjects' age ranged from 21 to 30 years; 18 women were primigravida. None of the women had any pregnancy- (e.g. hypertensive disorders, intrauterine growth retardation, infections) and nonpregnancy-related diseases, pharmacological treatment during pregnancy or anesthesia during oxytocin-induced labour. All the pregnancies were single.

Hormone assays

The plasma concentrations of CRH and DHEA were measured by radioimmunoassays (RIA) according to the procedure provided by the companies (CRH – Peninsula Labouratories Inc., USA, DHEA – Immunotech, France), assays were performed in duplicate. The intra-and interassay coefficients variation for DHEA were 4.5% and 5.8%, for CRH 3.8% and 8.2% respectively.

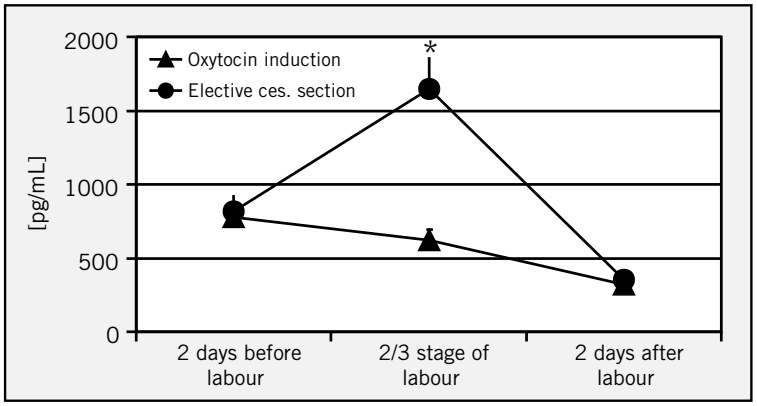
The concentrations of ACTH, DHEA and cortisol were estimated in duplicate by ELSA-ACTH – immunoradiometric assay obtained from CIS bio International ORIS Group, France. The intra- and inter-assay coefficients of variation were 2.9%, 3.1% and 5.3%, respectively.

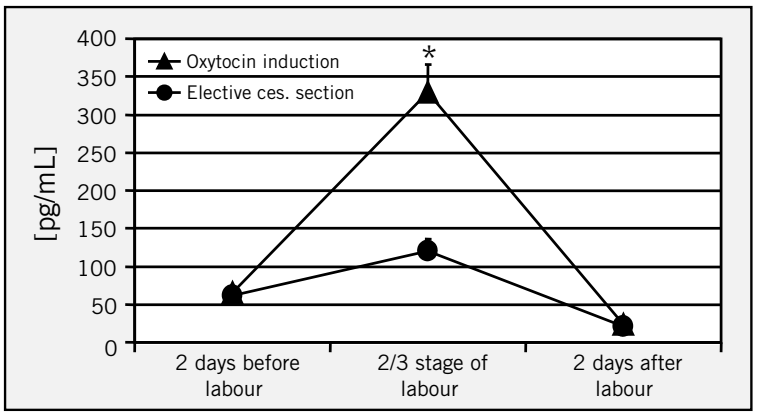
Analysis

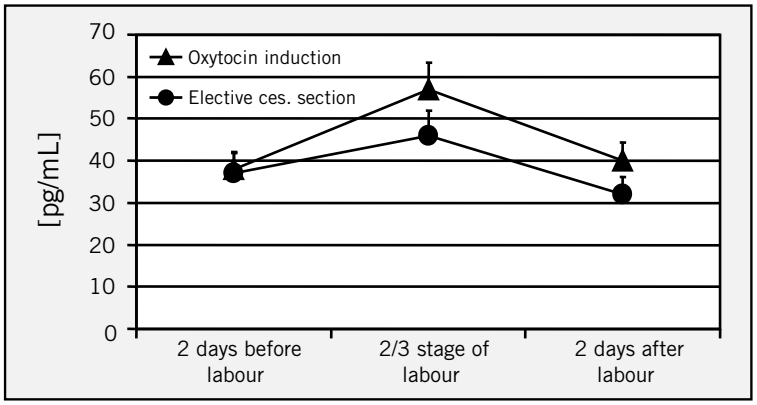
All results are reported as means ± SEM. Comparison of means (by *t-test*) were performed in the analysis of CRH and ACTH levels because they fit a Gaussian distribution. Comparison of means within the groups in three time points were tested using Repeated Measures Analysis of Variance, from package Statistica. Association between variables were assessed by correlation.

Results

Plasma CRH levels measured before labour in both groups were similar, 780 ± 58 pg/ml and 820 ± 78 pg/ml, respectively. During labour after oxytocin infusion CRH concentration modestly declined, to 624 ± 83 pg/ml, but was in group of women with elective t cesarean section went up (1650 ± 189 pg/ml). Forty-eight hours after labour there was no difference between the groups. The mean final plasma levels was 335.5 ± 57 pg/ml (Fig. 1). The mean plasma ACTH prior to the delivery was at the same level in all subjects, 65 ± 9.2 pg/ml, and 62 ± 8.4pg/ml respectively. Measured during the third stage of labour ACTH rose in the group with oxytocin infusion, to 330 ± 65 pg/ml, and it differ statistically to the level observed in the group with elective cesarean section – 120 ± 44 pg/ml After the delivery, the hormone concentration dropped to the level observed before labour (21 ± 2.4 pg/ml/) (Fig. 2). The concentrations of cortisol before delivery was similar in both groups, then rose to the same level during the delivery, and 48 hour after labour remained at the level observed before delivery (Fig. 3). The DHEA concentration was similar in both groups, did not change during the labour, there was no difference between its level in the umbilical vein and artery. In the group with oxytocin-induction there was no correlation between maternal CRH and ACTH or cortisol concentration, but such a correlation occurred in the group with elective cesarean section. The level of CRH in umbilical vein was statistically higher than in artery (data not shown). The concentration of ACTH and DHEA in umbilical artery was similar in both groups. Interestingly, the concentrations of CRH and cortisol in umbilical artery in group of newborns delivered after elective cesarean section were statistically higher then in other group (Fig. 4). None of the examined obstetric variables (duration of labour, weight, length and biochemical parameters of newborn) were correlated with changes in hormone concentration.







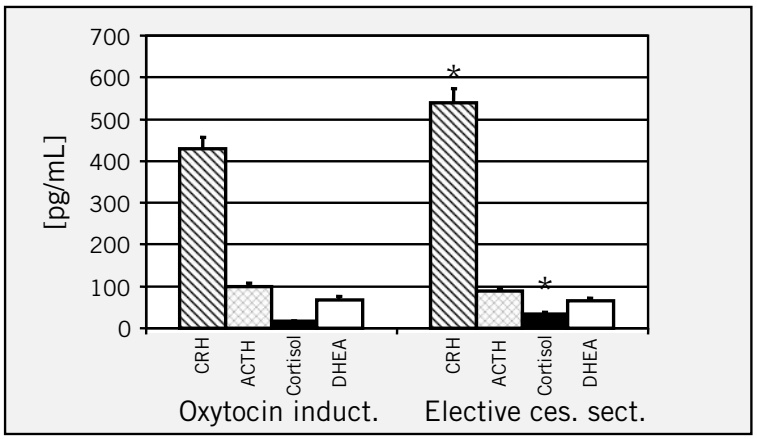


Fig. 1. The changes in CRH concentration in maternal serum before labor, during the third stage of labor and on the second day after labor. The asterisk means statistical significance between the groups, $p < 0.02$, the results were shown as mean ± SEM.
Fig. 2. The changes in ACTH concentration in maternal serum before labor, during the third stage of labor and on the second day after labor. The asterisk means statistical significance between the groups, $p < 0.02$, the results were shown as mean ± SEM.
Fig. 3. The changes in cortisol concentration in maternal serum before labor, during the third stage of labor and on the second day after labor. The asterisk means statistical significance between the groups, $p < 0.02$, the results were shown as mean ± SEM.
Fig. 4. The changes in CRH and ACTH in umbilical vein and artery, blood was sampled immediately after the placenta was born. Oxytoc.- oxytocin-inducted labor, Elect.- elective cesarean section. The asterisk means statistical significance compared between the groups,
$p < 0.05$, the results were shown as mean ± SEM.

Discussion

There is a considerable evidence that the maternal HPA axis is altered during pregnancy [9]. Concentration of plasma cortisol is increased and resistant to the suppressive effects of dexamethasone [4]. The activity of the HPA axis during parturition itself, however, has gained very little attention until now. Our earlier work, however showed that maternal HPA axis can answer the stress stimuli, like operative labour, although, their function rather depends on hypothalamic CRH or other factors circulating within the portal circulation system of the pituitary than on CHR from placental origin [10,11]. The elevated concentration of placental CRH preclude to estimate the changes in the functioning of the maternal HPA axis and the mother's hypothalamus secretion. These results are in accordance with work of Magiakou et al. [13], suggesting that the maintenance of circardian rhythmicity of ACTH is due to the AVP rather than to CRH levels. Our data confirm also report by Reis et al who showed lower levels of CRH before labour without spontaneous contraction [3]. In our earlier work we did not find the correlation between levels of CRH and ACTH and cortisol in plasma of women delivered spontaneously and by the way of cesarean section conducted due to the hypoxia of the fetus [data unpublished], and between CRH and ACTH during induction of oxytocin [10]. Present study confirm the earlier finding about lack of correlation between CRH, ACTH and cortisol during the parturition, but only in group delivered after oxytocin infusion, similarly to the results of Bergant and al. [14]. In group delivered by the elective cesarean section concentrations of all hormones of the maternal HPA axis were positively correlated, suggesting that suppression of maternal HPA axis may be partially due to the psychological stress factors, then to surgical intervention.

Unlike to the other authors we have observed high of CRH during the labour only in case of operative labour [3,11,14,15]. Elective cesarean section, as well as cesarean section conducted the course of labour, showed the CRH concentration remained at the same levels [data unpublished, Fig 1]. In case of elective cesarean section, the mid-labour concentration of this hormone was elevated in comparison to the values observed before level. When the labour continuities in physiological way the concentration of CRH declined during the labour (Fig1). Based on this observations we can conclude the high concentrations of CRH are due rather to the surgical stress then to the any event occurred during labour, that can caused rapid release of CRH, probably from placenta, rather from hypothalamus. These results may also suggest that labour can progress without an increase in placental CRH secretion. The hypothalamic CRH, like many hormones produced and released by hypothalamus (e.g. TRH and somatostatin), is difficult to measure peripherally, in most cases we can detect only the same peptides synthesized and released by peripheral organs like the placenta, gut or heart. The proper hypothalamic function in pregnancy is difficult to estimate due to the high levels of placental CRH.

Interesting observation concerns the elevated level of ACTH in the group of oxytocin infusion. This might be correlated with oxytocin influence on the modulation of anterior pituitary secretion. It is known that oxytocin stimulates LH, PRL and ACTH release from anterior pituitary [16,17]. However, this peptide directly only weakly stimulates ACTH release, but potentates the rCRH-stimulated ACTH release both in vivo and in vitro [16,18]. On the other hand, it is suggested that during the late pregnancy and parturition due to the higher oxytocin plasma levels, the general activity of the oxytocin system is highly activated [19]. The very high concentration of ACTH observed in the group receiving oxytocin treatment might possibly have a similar mechanism, with the primary stress response being amplified by oxytocin. Despite of highly elevated level of ACTH in group with oxytocin induction time-course and concentrations of cortisol secretion did not change in comparison to the group which underwent elective cesarean section, showing that even so high increase in ACTH concentration does not result in stimulation of adrenal function.

Newborns HPA-axis in comparison to mother's, however, responded differentially to the way of parturition or oxytocin infusion. Since 12 week of gestation, fetal pituitary-adrenal axis can be controlled by CRH from the fetal hypothalamus, but it has also been suggested that high levels of placental CRH can stimulate fetal pituitary-adrenal axis [20,21], as well as fetal hormones can influence the hormonal activity of placenta [15]. In the present study seems not to be surprising that in newborns delivered in the way of elective cesarean section concentrations of CRH and cortisol were higher then in group after oxytocin induction, despite of the similar concentration of ACTH in both groups (Fig.4). The question raises if the higher concentration of cortisol depends of stronger stimulation of fetal HPA axis but operative way of deliver, but this hypothesis is not support by not–elevated concentration of ACTH. The concentration of cortisol observed by us in earlier studies were similar to the levels observed in group after oxytocin induction, we can thus assume that this is „normal" cortisol level observed after the delivery. The unexpected high concentration of this hormone in the group with elective cesarean section might be due to the decreased stress factors, despite of operative labour. The psychological preparation of mother for the time and date of delivery, lack of contractions and anesthesia preparation may have significant importance in this case and resulted in „saving" the cortisol by newborn or mother. As circulating CRH in fetus is almost exclusively of placental origin, in nonhuman primate cortisol in fetus appears to be of maternal origin [17]. On the other hand, in sheep, placental CRH stimulates fetal HPA axis which, in turn, leads to a surge of fetal cortisol secretion [15,17]. It is worth to underline, that in newborns born after oxytocin infusion we did not observed elevation of ACTH, as in mothers. It clearly suggests that fetus and mother HPA are not in parallel

stimulated or did not answer in the same way to the exogenous stimuli.

In summary, during the parturition the activity of the mother's HPA axis might be partially inhibited, but rather by psychological stressors factor as expectation of pain, emotional adjustment or preparation to the birth, rather then events connected with mode of parturition. The newborn's HPA axis respond differentially to mother's one. The ability of mother's HPA and newborn to answer is possibly related to many other factors then placental hormones of HPA axis, such as prolactin or endogenous opioids, as well as individual variations in plasma concentration of estrogen and progesterone levels. It is need to consider effects of central CRH and ACTH on the fine-tune regulation of HPA axis in the late pregnancy and parturition, not detectable due to the high levels of placental hormones.

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REFERENCES

1 Orth DN. Corticotropin-releasing hormone in humans. Endocrine Rev 1992; **13**:164–91.
2 Hillhouse EW, Gramatopoulos D, Milton NGN, Quartero HWP. The identification of human myometrial corticotropin–releasing hormone receptor that increases in affinity during pregnancy J Clin Endocrinol Metabol 1993; **76**:736–41.
3 Reis FM, Fadalti M, Florio P, Petraglia F. Putative role of placental corticotropin-releasing factor in the mechanism of human parturition. J Soc of Gynaecol Invest 1999; **6**:109–18
4 Smith R. Alterations in the hypothalamic pituitary adrenal axis during pregnancy and the placental clock that determines the length of parturition. J Reprod Immun 1998; **39**:215–20.
5 Schulte HM, Weisner D, Allolio B. The corticotropin releasing hormone test in late pregnancy: lack of adrenocorticotropin and cortisol response. Clin Endocrinol 1990; **33**:99–106.
6 Messiano S, Jaffe RB. Developmental and functional biology of the primate fetal adrenal cortex. Endocrine Rev 1997; **8**: 378–403.
7 Rose JC, Schwartz J, Green J, Kerr DR. Development of the corticotropin-releasing factor adrenocorticotropic hormone/β-endorphin system in the mammalian fetus. In: Polin RA, Fox WW. Editors. Fetal and neonatal physiology. 2nd ed. Philadelphia: WB Saunders 1998. p. 2431–41.
8 Smith R, Cubis J, Brinsmead M, Lewin T, Singh B, Owens P, et al. Mood changes, obstetric experience and alterations in plasma cortisol, beta-endorphin and corticotropin releasing hormone during pregnancy and the puerperium. Journal of Psychosomatic Research 1990; **34**:53–69.
9 Goland RS, Conwell IM, Warren WB, Wardlaw SL. Placental corticotropin-releasing hormone and pituitary-adrenal function during pregnancy. Neuroendocrinology 1992; **56**:742–9.
10 Ochedalski T Zylinska K, Laudanski T, Lachowicz A. Corticotropin releasing hormone and adrenocorticotropin levels in maternal and fetal blood during spontaneous and oxytocin-inducted labour. Eur J of Endocrinol 2001; **144**:1–6.
11 Ochedalski T, Zylinska K, Lachowicz A. Modulacja osi podwzgorze-przysadka-nadnercza podczas stresu zwiazanego z porodem. [(Modulation of hypothalamo-pituitary axis by stress during labour.) (In Polish with English abstract)] Ginekologia Polska 2002;**77**:1199–204.
12 Goland RS, Jozak S, Conwell I. Placental corticotropin-releasing hormone and the hypercortisolism of pregnancy. Am J Obstet Gynecol 1994; **171**: 1287–91.
13 Magiakou MA, Mastarakos G, Robin D, Margioris AN, Dubbert B, Calogero AE, et al Placental CRH secretion and the maternal hypothalamic-pituitary-adrenal axis in human pregnancy. Clin. Endocrinol (Oxford) 1996; **44**:419–28.
14 Bergant AM, Kirchler H, Heim K, Daxenbichler G, Herold M, Schrocksnadel H. Childbirth as a biological model for stress? Gynecol. Obstet. Invest. 1998;**45**:181–4.
15 Mastorakos G, Ilias I. Maternal hypothalamic-pituitary-adrenal axis in pregnancy and postpartum period. Postpartum related disorders. Ann NY Acad Sci 2000; **900**:95–106.
16 Deloof S, Montel V, Chatelain A. Effects of rat corticotropin-releasing factor, arginine vasopresin and oxytocin on the secretion of adrenocorticotropic hormone and corticosterone in the fetal rat in late gestation: in vivo and in vitro studies. Eur J Endocrinol 1994; **130**:313–9.
17 Mastorakos G, Ilias I. Maternal and fetal hypothalamic-pituitary-adrenal axis in pregnancy and the postpartum. Ann N Y Acad Sci 2003; **997**:136–49.
18 River C, Vale W. Effects of corticotropin releasing factor, neurohypophyseal peptides and catecholamines on pituitary function. Fed Proc 1985; **44**:195–8.
19 Higuchi T, Takodoro Y, Honda K, Negoro H. Detailed analysis of blood oxytocin levels during suckling and parturition in the rat. J Endocrinol 1986; **110**: 251–6.
20 Nodwell A, Carmichael L, Fraser M, Challis J, Richardson B. Placental release of corticotropin-releasing hormone across umbilical circulation of the human newborn. Placenta 1999; **20**: 197–202.
21 Fisher DA. The unique endocrine milieu of the fetus. J Clin Invest 1986; **78**:603–11.