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### **The onset of human labor: current theories.**

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Innovative research has led to marked improvement in medical knowledge. Advances in technology have allowed us to attain a clearer understanding of many physiologic processes. Despite these impressive gains in knowledge, the cause of the initiation of the process of human labor remains unclear. Potential factors include changes in hormonal levels of estrogen and progesterone, increased production of prostaglandins, and elevation of levels of corticotropin-releasing hormone, as well as increased sensitivity of the myometrium to endogenous oxytocin. It is most likely that interactions between these factors play an essential role in the process of labor, but the precise mechanism of onset still eludes us.

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### **The transition from fetus to neonate--an endocrine perspective.**

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The transition from fetus to neonate involves three phases: late gestation, parturition and the processes needed to establish independent homeostatic regulation after separation from the placenta. These phases are regulated by a series of fetal and placental endocrine events. Glucocorticoids have an important role in the preparation for birth, including involvement in lung and cardiac development, and the maturation of enzymes in a variety of pathways. Fetal cortisol production is, in turn, also under hormonal control. Parturition is a complex process, which is still poorly understood in humans. The final steps are largely dependent on the effect of prostaglandin F<sub>2</sub> alpha on the myometrium associated with increased oxytocin activity.

The transition to birth is accompanied by changes in respiration, circulation, glucose homeostasis, and the onset of independent oral feeding and thermoregulation. Several examples of endocrine components of the transition from fetal to neonatal life are reviewed here: the role of prostanoids, the onset of thermogenesis, and changes in the thyroid hormone and growth hormone axes. The effects of hormone levels on prematurity and growth retardation are also discussed.

*J Nurs Meas 1998 Winter;6(2):155-74*

### **Methodologic issues in the measurement of oxytocin in human neonates.**

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Oxytocin's (OT) role in the onset and maintenance of labor and in the letdown reflex is well known. OT also has been recognized as a neurotransmitter having functions in the central nervous system, including an influence on behavior (e.g., initiation of maternal behavior).

This research was conducted to (1) evaluate whether human tactile contact in the human newborn would increase urine OT levels and alter infant behavioral state, and (2) determine the reliability of measuring OT in human infant urine. Although the data did not support the hypotheses, it was noted that OT levels significantly decreased in infants who cried during the study period and that there was no correlation between infant's chronologic age and OT levels.

The findings illustrate several methodologic and measurement problems in the study of OT in human infants and that urine sampling in the neonate is not the most reliable method to evaluate change in OT levels. Some general issues concerning research with human infants also are discussed. Further research is recommended to document baseline levels of OT in neonates and to explore the use of salivary OT to measure short-term responses to interventions.

*Biol Reprod 1998 Apr;58(4):971-6*

**Morphine inhibits nocturnal oxytocin secretion and uterine contractions in the pregnant baboon.**

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Morphine is a potent inhibitor of nocturnal uterine contractions (UCs) in the pregnant baboon, and these contractions are known to be induced by oxytocin (OT). The purpose of this study was to determine the mode of action of morphine in inhibiting nocturnal UCs by examining the effect of morphine on OT secretion, OT clearance, and uterine responsiveness to OT. A tethered pregnant baboon model during the last third of gestation was used for these experiments.

In study 1, the effects of morphine or control saline on OT release and on spontaneous nocturnal UCs were examined. Study 2 determined the effects of morphine or control saline on the pharmacokinetics of OT after a bolus injection of OT. To exclude/include direct opiate effects on UCs, study 3 examined the responsiveness of the uterus to exogenous OT after morphine or control saline administration. Plasma OT levels were analyzed by RIA after extraction. UCs were assessed by frequency, amplitude, duration, and area under the curve. During nocturnal UCs, morphine, but not saline, administration resulted in the precipitous suppression of integrated OT levels ( $p < 0.05$ ) to 42% of pretreatment values at 0-15 min postinjection and 17% at 30-45 min. Simultaneously, UCs were significantly suppressed ( $p < 0.05$ ) by 75% at the 30- to 45-min interval. By 1 h, 5 of 7 animals showed no UCs. In study 2, morphine consistently increased the metabolic clearance rate (MCR) of OT in all trials ( $p < 0.05$ ), although the magnitude of this effect was small (median 9%). Finally, study 3 demonstrated that myometrial responsiveness to the challenge of exogenous OT was not depressed by opiate administration ( $p > 0.05$ ).

To summarize, the decrease in nocturnal UCs after morphine is primarily due to an inhibition of OT release, and perhaps, but to a much lesser extent, an increase in OT MCR. There was no evidence of a direct tocolytic effect of morphine on the uterus. In conclusion, opioids such as morphine are potent inhibitors of nocturnal UCs and act by suppressing OT release in the pregnant baboon.

*Obstet Gynecol 1997 Jun;89(6):918-24*

**Sex steroid receptors and human parturition.**

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**OBJECTIVE:** To investigate the correlation between sex steroid hormones and their receptors during normal and dysfunctional labor.

**METHODS:** Myometrial and decidual biopsies along with maternal and cord blood samples were taken from women with or without labor activity. Estrogen and progesterone receptor contents in myometrium and decidua were determined by enzyme immunoassay, and hormone concentrations were analyzed by radioimmunoassay.

**RESULTS:** In the lower segment of the uterus, the progesterone receptor concentrations of myometrium were significantly lower in oxytocin-resistant dystocia compared with those of normal labor and before labor ( $P < .04$ ,  $P < .005$ , respectively). No significant difference was found in the estrogen receptors contents in the groups studied. The progesterone receptors of myometrium from the upper segment showed higher concentrations in active labor compared with those before labor and oxytocin-resistant labor ( $P < .01$ ,  $P < .05$ , respectively). Estrogen receptors from the upper segment showed no significant

difference in these regards. There was no difference in peripheral and myometrial sex hormone levels in the groups studied.

CONCLUSION: These data suggest that, in the human, 1) oxytocin-resistant labor is associated with low levels of progesterone receptors, 2) estrogen receptors content in myometrium might have no or little relation to labor, and 3) functional labor seems not to be related to a decreased progesterone activity in the myometrium.

*Acta Obstet Gynecol Scand 1995 Aug;74(7):530-3*

### **Elevation of oxytocin levels early post partum in women.**

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BACKGROUND. The aim of this study was to determine plasma levels of oxytocin in women immediately after delivery.

METHODS. Oxytocin was measured in 18 healthy women at 15 minute intervals after normal vaginal deliveries with healthy infants. The mothers had their infants put skin-to-skin on their chests immediately after birth. The infants stayed there up to two hours post partum.

RESULTS. There were significant elevations of oxytocin 15, 30 and 45 minutes after delivery ( $p = 0.007$ ,  $0.02$  and  $0.02$  respectively) when compared with average pre partum levels sampled approximately 7-15 minutes before partus. This elevation of oxytocin coincided with the expulsion of placenta. In most women this first elevation was followed by repeated elevations of oxytocin. Oxytocin levels returned to pre partum levels at 60 minutes post partum.

CONCLUSIONS. Oxytocin is known to play a role in maternal bonding in animals. Earlier studies indicate that there is a sensitive period for bonding the first hour after giving birth even in women. Our study demonstrates a coincidence of this putative 'sensitive period' and high levels of oxytocin.

*Eur J Endocrinol 1994 Aug;131(2):167-72*

### **Corticotrophin-releasing hormone and beta-endorphin in labour.**

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The objectives of this study were to determine whether the maternal plasma corticotrophin-releasing hormone (CRH) concentration influences the amount of uterine contractility induced by infused oxytocin during induction of labour, and secondly to assess changes in CRH and beta-endorphin in response to stress during labour.

Serial plasma CRH and beta-endorphin measurements were made in 40 women undergoing induction of labour and correlated with uterine contractility, cervical dilatation, length of labour, analgesic usage and fetal distress. The plasma CRH concentration did not change throughout labour. In subjects receiving infused oxytocin there was a significant positive correlation between plasma CRH and the amount of uterine activity, and a high plasma CRH level was associated with shorter labour. The plasma beta-endorphin level rose with progressive cervical dilatation and fell after epidural anaesthesia. The plasma CRH level did not correlate with the plasma beta-endorphin level or rise with fetal distress.

We conclude that high levels of maternal plasma CRH are associated with an increase in the uterine contractile response to infused oxytocin. The maternal plasma CRH level does not vary in response to maternal or fetal stress, but beta-endorphin secretion does rise in response to the stress of labour and is influenced by pain perception.

### **Effects of lumbar epidural analgesia on prostaglandin F2 alpha release and oxytocin secretion during labor.**

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The concentrations of plasma oxytocin and prostaglandin F2 alpha metabolite (PGFM) were measured in 10 parturients with and 10 without lumbar epidural analgesia. A blood sample was taken immediately before analgesia and another 60 min later.

The control patients were matched for the stage of cervical dilatation at the time of the first blood sample; the second was drawn 60 min later. Plasma PGFM decreased significantly after lumbar epidural anesthesia and increased in controls resulting in a highly significant difference between the groups ( $P < 0.005$ ). Plasma oxytocin concentrations levels also changed in opposite directions in the two groups but the difference did not reach statistical significance ( $P < 0.1$ ).

Uterine activity increased in the controls and decreased in the analgesia group resulting in a significant difference between the groups ( $P < 0.05$ ). All subjects delivered vaginally. The total duration of labor was longer in the analgesia group (7.8 +/- 1.0 h vs. 4.7 +/- 0.6 h;  $P < 0.05$ ) as was the duration after analgesia (5.1 +/- 0.9 h vs. 2.5 +/- 0.8 h;  $P < 0.05$ ), whereas the duration of the second stage was not significantly different. We conclude that lumbar epidural anesthesia results in suppression of PGF2 alpha release which may be the cause of the diminished uterine activity and the prolonged duration of the first stage of labor.

*Clin Endocrinol (Oxf) 1992 Oct;37(4):349-53*

### **The effect of morphine and naloxone administration on plasma oxytocin concentrations in the first stage of labour.**

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**OBJECTIVE:** We investigated the effect of an opiate (morphine) and an opiate antagonist (naloxone) on the maternal secretion of oxytocin in the first stage of labour.

**DESIGN:** Patients were randomized to receive either morphine 5 mg (n = 9), naloxone 1.2 mg (n = 10) or sterile water (n = 9) which was injected intravenously.

**PATIENTS:** Healthy women in the first stage of labour between 3 and 6 cm dilated with no prior analgesia or oxytocin administration were recruited for the study.

**MEASUREMENTS:** Peripheral maternal oxytocin levels were measured by radioimmunoassay for 15 minutes before and 15 minutes after administration of the assigned substance. Sampling was at 2.5 minute intervals.

**RESULTS:** Significant reduction in the mean oxytocin concentration was found in the patients who received morphine (-2.62 pmol/l/sample) but no change was found in the naloxone group (+0.57 pmol/l/sample) when compared with controls (+0.64 pmol/l/sample).

**CONCLUSION:** Maternal oxytocin secretion is inhibited by exogenous opiates in the first stage of labour while an effect of opiate antagonism was not demonstrated.

*Baillieres Clin Endocrinol Metab 1990 Jun;4(2):333-49*

### **The endocrinology of parturition in the human.**

**Steer PJ.**

Current evidence suggests that oestrogens, progesterone, relaxin, the prostaglandins, and oxytocin are all hormones concerned to a major degree with the onset and maintenance of parturition. Oestrogens, relaxin, and the prostaglandins are particularly involved with cervical ripening, while prostaglandins, progesterone and oxytocin are more involved in regulating myometrial contractility. Catecholamines may also have some regulatory function in relation to uterine contractions. Progesterone dominance during pregnancy is

associated with a firm closed cervix, few myometrial gap junctions, low calcium levels in the cells, and a quiescent myometrium. At term, a change in the oestrogen/progesterone balance favours cervical ripening and increased uterine activity. Of particular importance at the level of the muscle cell are changes in the number of oxytocin receptors; a complex interaction between cAMP and phosphoinositide metabolism governs the intracellular level of calcium, thus regulating contractile activity.

*Life Sci 1990;47(1):57-65*

**Temporary peripartal impairment in memory and attention and its possible relation to oxytocin concentration.**

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The aim of the present study was to investigate peripartal performance on cognitive tests and its possible relationship with plasma oxytocin concentrations. Twenty women (cases) were tested on five experimental occasions, the first toward the end of pregnancy and the last 12 months postpartum.

On each experimental occasion performance on cognitive tests of memory and attention was recorded and oxytocin concentrations were simultaneously assayed in plasma-samples. Twenty non-pregnant women (controls) were investigated at similar intervals. Cases were found to have improved their performance on some cognitive tests significantly more than controls when results at 6 and 12 months after delivery were compared with those from the end of pregnancy and up to three months after partus.

This observation strongly suggests impairment in cognitive performance during the peripartal period. Cases had significantly higher oxytocin concentrations than controls in plasma samples up to three months post partum. No correlation was, however, found between cognitive test results and levels of oxytocin concentration.

*Am J Perinatol 1989 Apr;6(2):145-52*

**Fetal and maternal oxytocin in human parturition.**

**Chard T.**

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Measurements of oxytocin in maternal and fetal circulation during human labor are reviewed and related to known changes in uterine oxytocin sensitivity during pregnancy and labor.

It is concluded that oxytocin is secreted in short-lasting spurts; therefore levels measured with infrequent intervals do not give adequate information on the amounts of oxytocin secreted during labor. Presently, there is little evidence for an increased maternal secretion rate of oxytocin at the onset of labor, but during labor a progressive increase occurs, with a maximum at the expulsive phase. Fetal secretion rate also increases markedly during labor, but the timing of this increase is still unknown. The dramatic increase in human uterine oxytocin receptors at term makes the uterus responsive to very small amounts of oxytocin. Hence, an increased oxytocin secretion rate is not a necessary prerequisite for oxytocin-stimulated contractions during labor. Evidence from oxytocin receptor blockade and suppression of oxytocin secretion supports the concept that oxytocin is an important stimulus for uterine contractions in early human labor.

*Brain Res Bull 1988 Jun;20(6):743-9*

**Hypothalamic opioid mechanisms controlling oxytocin neurones during parturition.**

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The influences of opioids on oxytocin secretion and parturition were investigated in the rat. Morphine, administered centrally or peripherally, severely delays the course of established parturition. This delay is accompanied by reduced plasma oxytocin levels and is overcome by treatment either with the opioid antagonist naloxone, or by infusion of oxytocin. An endogenous opioid regulatory mechanism inhibiting oxytocin secretion becomes activated immediately prior to and during parturition. This mechanism does not operate earlier in pregnancy or during normal lactation and is not seen in nonpregnant animals. Naloxone acutely speeds up the course of established parturition, an effect accompanied by greatly elevated plasma oxytocin levels.

The mechanisms underlying opioid regulation of oxytocin neurones were investigated at two sites. Precipitated withdrawal from chronic morphine treatment causes hypersecretion of oxytocin. This response is mediated by greatly enhanced electrical activity in the perikarya of oxytocin neurones indicating the presence of opioid receptors on oxytocin neurones and/or on their afferent input. Opioid receptors are also present in the neurohypophysis where they exert direct and noradrenaline mediated effects on secretion from oxytocin terminals in vitro.

*Br J Obstet Gynaecol 1987 Jun;94(6):518-22*

### **A randomized control study of oxytocin augmentation of labour. 2. Uterine activity.**

**Bidgood KA, Steer PJ.**

Uterine activity was measured in 60 women whose first labour was progressing slowly in the active phase. The mean level of active contraction area (uterine activity integral, UAI) before oxytocin augmentation was 898 (SD 458) kPas/15 min. UAI increased significantly with time, even in women not given oxytocin. UAI increased logarithmically with increasing oxytocin infusion rate. Levels of uterine activity before and after oxytocin infusion are correlated positively such that the higher the initial level of UAI the higher the UAI in response to oxytocin. However, the regression line approaches the line of identity such that even with high doses of oxytocin UAI would not be likely to exceed 2500 kPas/15 min.

There is a positive correlation between uterine activity and cervical dilatation rate in unstimulated labour; however, this is less evident following oxytocin infusion. Increases in uterine activity below 1200 kPas/15 min result from both higher frequency and active pressure, whereas above 1200 kPas/15 min any increase is due mainly to a rise in frequency.

*Arch Gynecol Obstet 1987;241(1):13-23*

### **Oxytocin levels in maternal and fetal plasma, amniotic fluid, and neonatal plasma and urine.**

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Oxytocin was measured in maternal and fetal plasma, amniotic fluid and neonatal plasma and urine using a specific radioimmunoassay, following extraction procedures with Florisil.

Maternal oxytocin levels rose progressively with advancing gestation, but there were no significant differences between oxytocin levels around the onset of labor. No diurnal rhythm of oxytocin was evident in maternal plasma during the third trimester. Maternal and umbilical plasma oxytocin levels at spontaneous delivery were significantly higher than those at elective cesarean section. Maternal oxytocin levels in four cases of post-term delivery were lower than those during normal late pregnancy; all four cases experienced uterine inertia. All amniotic fluid samples had detectable oxytocin levels and there were no significant differences between oxytocin levels in the second trimester and those in the third trimester. Oxytocin levels in neonatal urine were higher than levels in amniotic fluid and lower than in the umbilical artery. Neonatal plasma oxytocin levels gradually decreased and oxytocin levels of 7-day-old infants were significantly lower than those in the umbilical artery, but higher than those in adults.

In conclusion, it appears that maternal oxytocin levels may not be involved in triggering the onset of labor but may play a role in the maintenance and reinforcement of labor.