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## **Mother and Newborn Adaptations after Birth:**

Influence of administration of oxytocin and  
epidural analgesia during labour

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## ABSTRACT

**Aims** This thesis explores postpartum physiological and psychological adaptations in mothers and newborns in the short- and long-term perspective. The thesis further explores the influence of labour ward interventions, such as epidural analgesia (EDA) and exogenous administration of oxytocin on these adaptations.

**Material and methods** An explorative longitudinal design was used. 72 healthy, non-smoking Swedish-speaking primiparae with a normal singleton pregnancy and birth and their healthy full term newborns were consecutively enrolled in the study. Mothers and newborns stayed together at the labour- and maternity wards and the newborns had been exclusively breastfed on demand. The mother-newborn dyads had been exposed to different labour ward routines: 1) mothers who had received intravenous oxytocin during labour (OT iv group, n=10), 2) mothers who had received oxytocin intramuscularly after birth to prevent postpartum haemorrhage but no other treatment (OT im group, n=15) and 3) mothers who had received EDA during labour (EDA group, n=24). 4) Mothers who had not received any form of oxytocin or EDA during labour (control group, n=23). The EDA group was divided into two separate groups: EDA with (EDA<sup>OT</sup> group, n=17) or without oxytocin infusion (EDA<sup>non-OT</sup> group, n=7). Data were collected two days postpartum in connection with a morning breastfeed. Maternal blood samples were drawn with an interval of 30 seconds during the first 7.5 minutes and at 10, 20, 30, and 60 minutes after start of suckling. These samples were analysed for oxytocin and prolactin using ELISA (I). Blood pressure was recorded by a wrist blood pressure monitor before and at 10, 30, and 60 minutes after start of breastfeeding. 33 mothers continued to measure their blood pressure once per week in connection with a breastfeed during a 6-month follow up (II). The women's personality profile was assessed at two days, two and six months postpartum by the Karolinska Scales of Personality (KSP) (III). The newborn interscapular skin temperature was recorded with an electronic thermometer before and at 5, 10, 20, and 30 minutes after start of the breastfeed (IV).

**Results** *Breastfeeding two days postpartum.* Breastfeeding induced an immediate pulsatile release of oxytocin and prolactin levels rose significantly after 20 minutes. There was a positive correlation between oxytocin and prolactin levels (I). Maternal systolic and diastolic blood pressure fell during the breastfeed by 9 and 8 mmHg, respectively (II). At two days postpartum, according to the KSP, the maternal personality profile was changed towards reduced anxiety and aggression and increased socialisation when compared to a normative sample of women (III). The interscapular skin temperature of the newborns rose during the breastfeed (IV). *Follow up study.* Blood pressure fell in response to breastfeeding episodes and basal systolic and diastolic blood pressure fell by 15 and 10 mmHg, respectively, during the 6-month follow up period (II). KSP ratings showed that the breastfeeding women exhibited lower scores on anxiety and aggression and higher scores on socialisation at two and six months postpartum, when compared to the normative sample of women (III). *Medical interventions during labour.* Median oxytocin levels were lower in the group of women having received EDA with oxytocin infusion (EDA<sup>OT</sup> group) than in the EDA<sup>non-OT</sup>, OT iv and OT im groups. In addition, median oxytocin levels were decreased in a dose-dependent manner in women having received oxytocin infusion in connection with labour (OT iv and EDA<sup>OT</sup> groups). Prolactin levels did not rise in women belonging to the EDA<sup>non-OT</sup> group, but rose more and at an earlier time point in mothers having received oxytocin infusion (OT iv and EDA<sup>OT</sup> groups) than in controls (I). The administration of EDA attenuated changes in the KSP towards less anxiety and more socialisation at two days post partum as seen in the control, OT iv, and OT im groups. At two and six months postpartum, however, the KSP scores of the EDA group had approached the KSP scores of the other groups. Exogenous oxytocin infusion (OT iv and EDA<sup>OT</sup> groups) dose-dependently reinforced the KSP changes in some anxiety and aggression subscales (III). Newborns to mothers who had received EDA during labour did not show a rise in interscapular skin temperature in response to breastfeeding, but the response was reinforced in newborns to mothers belonging to the OT iv group, when compared to controls (IV).

**Conclusion** This study confirms the existence of physiological and psychological adaptations in breastfeeding mothers and their newborns in the short- and long-term perspective. Administration of exogenous oxytocin and EDA during labour influenced these adaptations.

**Keywords** blood pressure, breastfeeding, epidural analgesia, labour, maternal personality pattern, newborn temperature, oxytocin, postpartum, prolactin, skin-to-skin contact.



## PUBLICATIONS

This thesis is based on the following articles, which will be referred to by their Roman numerals:

- I. Jonas, W., Johansson, L. M., Nissen, E., Ejdebäck, M., Ransjö-Arvidson, A. B., Uvnäs-Moberg, K. Effects of intrapartum oxytocin administration and epidural analgesia on the concentration of plasma oxytocin and prolactin, in response to suckling during the second day post partum.

*Breastfeeding Medicine* 2009; **4**, 71-82.

- II. Jonas, W., Nissen, E., Ransjö-Arvidson, A. B., Wiklund, I., Henriksson, P., Uvnäs-Moberg, K. Short- and long-term decrease of blood pressure in women during breastfeeding.

*Breastfeeding Medicine* 2008; **3**, 103-9.

- III. Jonas, W., Nissen, E., Ransjö-Arvidson, A. B., Matthiesen, A. S., Uvnäs-Moberg, K. Influence of oxytocin or epidural analgesia on personality profile in breastfeeding women: a comparative study.

*Archives of Women's Mental Health* 2008; **11**, 335-45.

- IV. Jonas, W., Wiklund, I., Nissen, E., Ransjö-Arvidson, A. B., Uvnäs-Moberg, K.

Newborn skin temperature two days postpartum during breastfeeding related to different labour ward practices.

*Early Human Development* 2007; **83**, 55-62.

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## LIST OF ABBREVIATIONS

ACTH	Adrenocorticotrophic hormone
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
CCK	Cholecystokinin
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CNS	Central nervous system
CRF	Corticotropine releasing factor
CS	Caesarean section
CSF	Cerebrospinal fluid
DBP	Diastolic blood pressure
DMX	Vagal dorsal motor nucleus
EDA	Epidural analgesia
EDA <sup>non-OT</sup>	Epidural analgesia <i>without</i> oxytocin infusion
EDA <sup>OT</sup>	Epidural analgesia <i>with</i> oxytocin infusion
ELISA	Enzyme-Linked Immunosorbent Assay
HPA axis	Hypophyseal-pituitary-adrenal axis
IU	International unit
KSP	Karolinska Scales of Personality
LC	Locus coeruleus
NA	Nucleus accumbens
NTS	Nucleus tractus solitarius
PAG	Periaqueductal gray
PVN	Paraventricular nucleus
OT	Oxytocin
OT im	Oxytocin administered intramuscularly
OT iv	Oxytocin administered intravenously
PIF	Prolactin inhibiting factor
r	Pearson's correlation coefficient
r <sub>s</sub>	Spearman rank correlation coefficient
RN	Raphe nuclei
SBP	Systolic blood pressure
sd	Standard deviation
SE	Standard error of the mean
SON	Supraoptic nucleus
VIP	Vasoactive intestinal peptide

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Papers I-IV

## **1 BACKGROUND**

Short- and long-term effects on maternal and newborn physiology and behaviour can be induced during the course of labour and the breastfeeding period. Both skin-to-skin contact between mothers and their newborns and suckling have been shown to promote interaction within the mother-infant dyad, to induce anti-stress effects in both mothers and newborns and to stimulate growth and development in the offspring. The period immediately after birth, “the early sensitive period”, seems to be of particular importance for inducing these effects.

Administration of some types of pharmacological pain relief during labour has been shown to delay mother and newborn interaction after birth. Further, Caesarean sections (CS) have been shown to attenuate some aspects of the development of maternal and infant adaptations.

A literature review of previous findings relevant for the topics mentioned above will be given. Since oxytocin seems to play an important integrative function during labour, the postpartum and breastfeeding periods, a presentation of oxytocin and its effect pattern will be given.



## **PHYSIOLOGICAL AND PSYCHOLOGICAL ASPECTS OF PREGNANCY, LABOUR, SKIN-TO-SKIN CONTACT AND BREASTFEEDING**

### **Oxytocin**

Oxytocin is a nonapeptide, which acts both as a hormone and a neurotransmitter. It is synthesized in the magnocellular neurons of the supraoptic nucleus (SON) and in the parvocellular and magnocellular neurons of the paraventricular nucleus (PVN) of the hypothalamus. From the magnocellular neurons, oxytocin is transported to the neurohypophysis to reach its target organs (uterus, mammary glands) via the circulation, where it has a half-life of one to two minutes (Ludwig and Leng 2006).

From the parvocellular neurons, oxytocin is transported via axons to reach many regulatory areas within the central nervous system, such as other areas of the hypothalamus, the anterior pituitary, the amygdala, the dorsal vagal motor nucleus (DMX), the hippocampus, the locus coeruleus (LC), the nucleus accumbens (NA), the nucleus tractus solitarius (NTS), the periaqueductal gray (PAG), the Raphe nuclei (RN) and the spinal cord (Buijs et al. 1985) (Table 1). Oxytocin has a half-life of about 20 minutes in the central nervous system (CNS) (Burbach et al. 2006, Ludwig and Leng 2006, Richard et al. 1991) and it is often broken down into smaller active fragments before binding to receptors to induce effects in the CNS (Stancampiano et al. 1991).

Oxytocin is produced in the cell bodies of the nerve cells and is then transported via the axon to be released into the circulation to exert hormonal effects or into the synaptic cleft to exert neurogenic effects. In addition to these modes of oxytocin release, evidence has shown that oxytocin can also be released directly from cell bodies and the dendritic part of the neurons within the PVN and SON, which may then result in diffusion of oxytocin to nearby and distant targets in the brain. Oxytocin may thus have an effect in areas that are richly provided with oxytocin receptors, even though very few, if any, oxytocin nerves lead to these areas. Accordingly, during the intense stimulation of the oxytocin producing cells that occur in connection with labour and suckling, the entire brain may be flooded with oxytocin (Ludwig and Leng 2006).

**Table 1.** Example of areas of the brain that are innervated by oxytocin containing nerves.

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Amygdala	Almond-shaped cell group located within the medial temporal lobes of the forebrain. It belongs to the limbic system and is linked to control of emotional reactions and memories.
DMX	The dorsal vagal motor nucleus (DMX) is located in the brainstem and is the main motor nucleus of the vagus nerve and contains cholinergic cell bodies. The nerve fibres originating in the DMX project, e.g. to the heart, gastrointestinal tract and lungs.
Hippocampus	The hippocampus is located within the medial temporal lobe of the forebrain and belongs, as the amygdala, to the limbic system. The hippocampus is important for memory and spatial orientation and also for processing information from sensory organs.
LC	The locus coeruleus (LC) is located in the brain stem and contains cell bodies of noradrenergic neurons and projects to most areas of the brain to exert excitatory effects. When the LC is activated alertness and aggression are stimulated. The LC integrates stress responses and is under inhibitory control of alpha-2-adrenoceptors.
NA	The nucleus accumbens (NA) is located in the forebrain. It plays a central role in the reward and reinforcement circuit. The main neurotransmitter is dopamine. Opioids can enhance the release of dopamine into the synaptic cleft.
NTS	The nucleus tractus solitarius (NTS) is located in the brainstem and is the major sensory nucleus of the vagal nerve. It processes afferent signals from organs of the body and forwards information to e.g. the paraventricular nucleus (PVN) of the hypothalamus. It is also an important regulatory centre of the activity of the sympathetic and parasympathetic aspects of the autonomic nervous system.
PAG	The periaqueductal gray (PAG) consists of a group of cell bodies located within the midbrain. It is important in pain modulation and in defence behaviours.
RN	The raphe nuclei (RN) consist of clusters of nerve cells in the brain stem and produce serotonin. Serotonergic nerves project to different areas in the brain and influence many functions, e.g. the levels of aggression, satiety and well-being.

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In situations of strong oxytocin release, such as labour and suckling, morphological and functional changes of the oxytocinergic system take place, both in the SON and PVN. The glial coverage of the oxytocinergic neurons retracts and the somatic/dendritic parts of the neurons become closer to each other allowing for interaction between these cells. The electrical action potential activity is thereby increased and the electrical firing activity of the magnocellular neurons becomes synchronised. Consequently, the electrical bursts are paralleled by a strong pulsatile release of oxytocin into the circulation (Hatton and Tweedle 1982, Theodosis et al. 1986).

Oxytocin is released in response to sensory stimuli such as parturition and suckling both into the circulation and the brain (Kendrick et al. 1986, Keverne and Kendrick

1994, Leng et al. 2008). Other sensory modalities, such as physical warmth, massage-like stroking and olfactory cues, can also induce the release of oxytocin (Agren et al. 1997, Lund et al. 2002, Stock and Uvnäs-Moberg 1988, Uvnäs-Moberg et al. 1993, Uvnäs-Moberg 1998a).

### **Effects of oxytocin**

Oxytocin may exert a multitude of physiological and behavioural effects depending on the dose and time schedule and experimental model used. The findings described below were obtained via animal experiments, but are of relevance for the present study and are summarized as follows.

#### *The hypophyseal-pituitary-adrenal (HPA) axis*

Generally, in response to a stressor, corticotropin releasing factor (CRF) is released from the PVN to stimulate the release of adrenocorticotrophic hormone (ACTH) in the adenohypophysis. Pituitary ACTH then induces a release of corticosterone (in animals) or cortisol (in humans) from the adrenal gland (Guyton and Hall 2002a). Following administration of oxytocin, corticosterone levels are lowered (sometimes following a short initial rise), suggesting a role for oxytocin in the inhibition of the HPA axis (Petersson et al. 1999a). Oxytocin acts at several sites of the HPA axis to decrease cortisol levels. It decreases the CRF secretion at the level of the parvocellular neurons in the PVN, it decreases the secretion of ACTH from the ACTH producing cells in the adenohypophysis, and it decreases the secretion of cortisol also at the level of the adrenal gland (Burbach et al. 2006, Neumann et al 2000, Petersson et al., Stachowiak et al. 1995). A long-term decrease of corticosterone levels occurs after repeated administration of oxytocin (Petersson et al. 1999a).

#### *Blood pressure*

Oxytocin has been shown to have a dual effect on blood pressure since it may induce either an increase or a decrease in blood pressure depending on the physiological circumstances (Petersson et al. 1999b). A decreased activity in cardiovascular-regulating aspects of the sympathetic nervous system is followed by a fall in blood pressure (Guyton and Hall 2002b). Oxytocin containing nerves from the PVN innervate the NTS (Buijs et al. 1983) – an area linked to regulation of blood pressure – and oxytocin may be released from nerve terminals in this area, e.g. in response to suckling

to decrease sympathetic nervous tone and thereby results in the lowering of blood pressure. After repeated administration of oxytocin, the decrease of blood pressure becomes sustained (Petersson et al. 1999b). Oxytocin increases the activity of alpha-2-adrenoceptors in the NTS, which subsequently attenuates the signalling function of noradrenalin and adrenalin in the brain (Petersson et al. 1998, Petersson et al. 2005a).

#### *Anxiolytic-like effect*

In rats, low doses of oxytocin give rise to an anxiolytic-like effect. This effect is exerted in the amygdale and is expressed behaviourally by increased curiosity towards the environment and higher social interaction with cage mates (Uvnäs-Moberg et al. 1994a). Knock-out mice lacking the oxytocin receptor are more anxious and more sensitive to stress than normal mice (Amico et al. 2004).

#### *Pain threshold*

Oxytocin increases nociceptive thresholds. Rats treated with oxytocin react with a longer latency in the tail-flick test. This effect may be exerted at different locations in the CNS, such as in the PAG and in the dorsal horn of the spinal cord. The effect of oxytocin on pain thresholds is mediated by the involvement of endogenous opioids (Petersson et al. 1996a, Petersson et al. 2005b).

#### *Storing and transfer of nutrients*

Oxytocin influences vagal efferent nerve activity. The release of gastrointestinal hormones is influenced by oxytocin and it promotes weight gain and growth. Glucose and glucagon levels are increased, and the release of glucagon may occur in response to activation of oxytocin receptors located on the alpha cells of the pancreas. The mammary gland has an increased number of insulin receptors to stimulate uptake of nutrients for milk production (Eriksson et al. 1994, Uvnäs-Moberg 1989).

#### *Behavioural effects of oxytocin in mammals*

Oxytocin stimulates several types of social behaviours in mammals. In particular, oxytocin seems to play a key role in the onset of maternal behaviour. At parturition, large amounts of endogenous oxytocin are released into the cerebrospinal fluid (CSF) and into plasma (Kendrick et al. 1986, Keverne and Kendrick 1994, Leng et al. 2008). Pedersen and Prange demonstrated that intracerebroventricular injections of oxytocin

were able to induce maternal behaviour in virgin rats when primed with oestrogen (Pedersen and Prange 1979, Pedersen et al. 1982), as defined by e.g. carrying of two or more pups in the mouth, licking of and crouching over pups, or nest building. In sheep, maternal behaviours that include low-pitch bleats, sniffing, licking and approaching/following the lamb, and bonding behaviours such as recognition, acceptance and preference for the own lamb, can be induced by direct oxytocin administration and by indirect vaginocervical stimulation, which results in oxytocin release (Kendrick et al. 1987). It has also been suggested that prolactin is involved in the initiation of maternal behaviour in mammals (Mann and Bridges 2001).

#### *Behavioural effects of oxytocin in humans*

There is support for a role of oxytocin in the regulation of human social behaviour. Intranasal oxytocin administration stimulates social interaction, reduces anxiety and attenuates cortisol responses to mental stress (Heinrichs et al. 2003, Kirsch et al. 2005). Both intranasal and intravenous administration of oxytocin caused improvement of social skills in the sense that the ability to interpret emotional contents of facial expressions and speech intonation was enhanced (Domes et al. 2007a and b, Hollander et al. 2007). Guastella et al. (2008) demonstrated an increase in the frequency and duration of gaze towards the eye region of human faces. Oxytocin has further been shown to increase trust in others (Kosfeld et al. 2005).

#### **Oxytocin acts via and interacts with other signaling systems**

It is generally well understood that oxytocin acts by influencing other signaling systems, such as the cholinergic, dopaminergic, noradrenergic, opioidergic and serotonergic systems. The role of oxytocin therefore seems to be a coordinator of the function of signalling systems in order to create optimal (and flexible) adaptive patterns, for example during labour and in the breastfeeding situation (Uvnäs-Moberg and Petersson 2005, Uvnäs-Moberg and Petersson 2009).

#### *Functional relationship between oxytocin and endogenous opioids*

There is a strong functional relationship between oxytocin and endogenous opioids that may act to stimulate oxytocin release in certain situations (Keverne and Kendrick 1991). But, most often oxytocin is under an inhibitory tone of opioids. For example, morphine given during parturition has been demonstrated to act centrally through

opioid receptors to inhibit oxytocin secretion and thereby impairing the expression of maternal behaviour (Russell et al. 1989). Conversely, naloxone, a morphine antagonist, increases the release of oxytocin during parturition (Russell et al. 1989).

#### *Oxytocin, bonding and dopamine*

Oxytocin has been shown to be involved not only in bonding between mother and young, but also between adult male and female voles. Dopamine is also involved in the bonding process and interacts closely with oxytocin in the NA (Insel 2003, Young 2009).

### **Role of oxytocin in human reproduction**

#### *Labour*

Labour consists of three stages. The first stage is characterized by the onset of regular uterine contractions, resulting in full dilatation of the cervix. During the second stage, contractions intensify and the mother actively pushes and the baby is born. During the third stage, the placenta is expelled. Normal labour lasts approximately 12 -15 hours in primiparae and 8-12 hours in multiparae.

The first effect ascribed oxytocin was its effect to induce uterine contractions (Dale 1906). Oxytocin-specific receptors permeate the myometrium, which increase in number and sensitivity during pregnancy (Fuchs et al. 1984) due to rising levels of oestrogens (Amico et al. 1981). Oxytocin binds to these receptors when stimulating uterine contractions.

During labour, oxytocin is released in pulses into the circulation, demonstrating variable amplitudes and intervals. The frequency of pulses increases during labour, and during the second stage of labour the frequency reaches about 6 pulses per 10 minutes (Fuchs et al. 1991). The increased frequency may be due to enhanced activation of the Ferguson reflex. Increasing pressure from the foetus' head stimulates nerve receptors in the pelvic floor, cervix and the upper portion of the vagina, which leads to activation of sensory neurons. These nerve impulses travel via afferent sensory neurons, the hypogastric and pelvic nerves in particular, via the spinal cord to reach the oxytocin producing cells in the hypothalamus of the brain to stimulate oxytocin release. When contractions increase, the pressure on the cervix increases and consequently more

oxytocin is released. A feed-forward system is activated (Ferguson 1941). In addition, during vaginocervical stimulation, by which oxytocin is released, pain sensitivity in women is reduced (Komisaruk and Sansone 2003).

#### *Oxytocin in the newborn*

In the newborn, oxytocin measurements have been made in the arteria of the umbilical cord in connection with birth. Some studies point out that newborns have higher oxytocin levels in comparison to their mothers after birth (de Geest et al. 1985, Sellers et al. 1981). Marchini et al. (1988) found significantly higher foetal oxytocin levels after vaginal birth than after CS.

#### *Early postpartum period*

If the healthy newborn is put in skin-to-skin contact on his/her mother's chest immediately after birth the newborn demonstrates an inborn sequence of pre-feeding and feeding behaviours (Widström et al. 1987). The baby seems to be guided by visual and olfactory stimuli (Varendi et al. 1994). In preparation for the breastfeed the baby touches and tastes the nipple, makes massage-like movements on the mother's breasts and starts to breastfeed at the age of about one hour, and about two hours postpartum, the baby falls asleep (Ransjö-Arvidson et al. 2001).

After birth, maternal oxytocin levels are elevated, in particular in connection with expulsion of the placenta, and remain elevated for about 45 minutes postpartum (Nissen et al. 1995). The massage-like movements mentioned above are followed by elevation of oxytocin levels, suggesting that activation of sensory nerves in part causes the release of oxytocin occurring postpartum (Matthiesen et al. 2001). Oxytocin released into the circulation may contribute to the increased maternal chest temperature observed during skin-to-skin contact (Bystrova et al. 2007a, Marshall et al. 1992).

The skin-to-skin contact calms both the mother and baby, and in fact, babies lying in close contact on their mother's breasts cry less than babies separated from their mothers (Christensson et al. 1992, Christensson et al. 1995). In addition, to inducing relaxation and calmness, skin-to-skin contact may also induce a pain relieving effect (Gray et al. 2000). These effects may involve by the oxytocin released in response to activation of cutaneous sensory nerves by warmth, touch, stroking and light pressure (Lund et al.

2002, Olausson et al. 1999, Stock and Uvnäs-Moberg 1988, Uvnäs-Moberg et al. 1993, Uvnäs-Moberg 1998a).

### *Breastfeeding*

During pregnancy, increased plasma concentrations of placental lactogens cause enlargement and development of the mammary glands; however, high levels of progesterone and possibly oestrogen inhibit milk production. When the levels of these hormones fall, following expulsion of the placenta, this inhibition is withdrawn. The peptide prolactin is then produced in the lactotroph cells of the adenohypophysis and is released after birth in response to the suckling stimulus to induce milk production. For maternal milk production, stimulation of somatosensory afferent nerves is required (Guyton and Hall 2002a, Lawrence and Lawrence 2002).

Prolactin release is regulated by many factors; for instance, it is inhibited by dopamine or prolactin inhibiting factor (PIF) released from the hypothalamus (Guyton and Hall, 2002a), while prolactin levels rise in response to each breastfeed. Basal prolactin levels fall, however, during the course of the breastfeeding period, indicating that prolactin is especially important for milk production in connection with initiation of breastfeeding (Battin et al. 1985, Johnston and Amico 1986). Of interest, basal prolactin levels recorded at 3-4 months postpartum predict the duration of the remaining period of breastfeeding (Uvnäs-Moberg et al. 1990a).

Ott and Scott demonstrated the role of oxytocin in milk ejection already in 1910 (Ott and Scott 1910). Suckling stimulates oxytocin release from the neurohypophysis into the circulation of the mother for the purpose of inducing milk ejection (Lincoln and Paisley 1982). When oxytocin levels are studied in connection with breastfeeding two days after birth, human mothers exhibit a pulsatile plasma oxytocin pattern. The number of oxytocin peaks during the first 10 minutes of breastfeeding correlated to the amount of milk ingested by the baby (Nissen et al. 1996).

Oxytocin also plays a role in milk production. Oxytocin reaches the prolactin-producing cells (lactotrophs) in the anterior pituitary via the hypophyseal portal vessels to stimulate prolactin release via oxytocin receptors (McKee et al. 2007, Samson et al.



1986). Evidence has shown that a lack of oxytocin hampers the release of prolactin in response to suckling (Samson et al. 1986).

### **Physiological and psychological adaptations in the mother and infant**

Mothers and their babies undergo adaptive physiological and psychological changes during labour, in the postpartum period and during breastfeeding. Below, a short review of such adaptive changes will be given regarding the function in the gastrointestinal tract, the HPA axis, the cardiovascular system and maternal psychological adaptations. Oxytocin released during labour, during skin-to-skin contact and during breastfeeding seems to play an important role in triggering and coordination of these effects.

#### *Gastrointestinal tract*

Studies conducted in both animals and humans show that during suckling, efferent vagal nerve fibres are activated, which induces a release of gastro-intestinal hormones. Gastrin, cholecystokinin (CCK) and insulin levels rise and lead to an optimized digestive process both in the mother and the offspring/infant (Eriksson et al. 1994, Uvnäs-Moberg 1994b, Uvnäs-Moberg 1989, Widström et al. 1988). The suckling related release of gastrointestinal hormones involves an effect of oxytocin in the brain (Björkstrand et al. 1996, Lindén et al 1990).

In contrast, the less intense sensory stimulation induced by skin-to-skin contact (in the absence of suckling and food) is followed by a decrease of the levels of gastrointestinal hormones, such as gastrin and CCK. These effects seem to be mediated by inhibitory vagal fibres and oxytocin seems to play an important regulatory role also in this situation. The release of gastrointestinal hormones in response to suckling and feeding is, however, reinforced by skin-to-skin contact (Törnhage et al. 1998).

#### *HPA axis*

Maternal cortisol levels fall during breastfeeding suggesting a decreased activity of the HPA axis (Amico et al. 1994, Heinrichs et al. 2002, Nissen et al. 1996) and skin-to-skin contact between mother and newborn contributes to this effect (Johansson et al. 2009). Cortisol levels also decrease in infants as a response to skin-to-skin contact (Gitau et al. 2002).

Oxytocin released by the sensory stimulation induced by suckling or in response to skin-to-skin contact decreases cortisol levels by decreasing the release of CRF in the hypothalamus and of ACTH in the anterior pituitary (Johansson et al. 2009). In a more long-term perspective, breastfeeding women demonstrate a reduced release of cortisol in response to physical activity (Altemus et al. 1995).

#### *Maternal blood pressure*

Maternal blood pressure is influenced by breastfeeding. Previous studies have demonstrated a decrease in systolic and diastolic blood pressure (SBP and DBP, respectively) in response to a breastfeeding session (Light et al. 2000, Nissen et al. 1996). Furthermore, postpartum lactating women have lower SBP when compared to non-lactating women during the first 6-24 weeks postpartum, suggesting that breastfeeding lowers blood pressure (Altemus et al. 2001).

Recent data indicate that pregnancy and/or breastfeeding may exert long-term cardiovascular effects in the mother. For instance, DBP was lower in multiparous women than in nulliparous women at term and in another study, where blood pressure was followed over three pregnancies in the same mother, both SBP and DBP were continuously lower during the second and third pregnancies than during the first pregnancy at comparable weeks of gestation (Strevens et al. 2001, Strevens et al. 2002).

It has also been demonstrated that lactation diminishes the risk for development of hypertension and incidence of myocardial infarction in women, an effect that is related to the total duration of breastfeeding (Lee et al. 2005, Stuebe et al. 2009). Together these data show that pregnancy and breastfeeding have positive effects on cardiovascular function and blood pressure in women.

#### *Psychological adaptations*

Maternal anxiety levels decrease during a breastfeeding episode (Heinrichs et al. 2001). In addition, mothers undergo more long-term adaptive psychological changes during labour, the postpartum and breastfeeding periods, where the personality profile of breastfeeding women is influenced. In addition, according to studies utilising the Karolinska Scales of Personality (KSP), a self-reporting inventory measuring personality traits (af Klinteberg et al. 1986, Gustavsson 1997a), breastfeeding women

become less anxious, more relaxed and prone to a calm lifestyle when compared to a normative sample of non-lactating women (Nissen et al. 1998, Uvnäs-Moberg et al. 1990b). These studies also report higher levels of socialisation. Such changes can be observed two to four days after birth in primiparae and in multiparae (Nissen et al. 1998), and have been interpreted as being meaningful from the perspective of the breastfeeding woman, since they may help her adapt to the demands of breastfeeding (Uvnäs-Moberg 1996).

Data further imply that oxytocin may play a role for the maternal psychological adaptations. Negative and positive correlations between scores obtained in the subscales of the KSP related to anxiety and social competence, respectively, and the levels/pattern of oxytocin during a breastfeed two to four days after delivery have been demonstrated in mothers (Nissen et al. 1998, Uvnäs-Moberg et al. 1990b).

In addition, mothers who breastfeed interact more with their babies and hold them more often (Wiesenfeld et al. 1985) and touch and smile towards them more than bottle feeders do during the first eight weeks postpartum (Dunn and Richards 1977). They also express more positive mood and less anxiety and stress (Groër 2005).

#### *Maternal bonding and attachment*

High circulating oxytocin levels during late pregnancy are correlated with prolonged breastfeeding duration (Silber et al. 1991). Furthermore, recent studies indicate that oxytocin also takes part in the process of maternal-infant interaction and bonding behaviours (Feldman et al. 2007, Levine et al. 2007). Not only oxytocin but also prolactin and glucocorticoids have been suggested to enhance maternal behaviour postpartum (Fleming 1997, Mann and Bridges 2001).

#### *Regulation of temperature in mothers and their newborns*

Here, as relevant to the present study a short review on the effects on infant temperature will be given.

*In utero*, the placenta is responsible for thermoregulation of the foetus, and foetal temperature follows maternal temperature; whereas after birth, the newborn regulates its own temperature. Newborns are extremely sensitive to heat loss and have difficulties

in obtaining thermal equilibrium since the surface-to-weight ratio of the newborn is rather high (Rutter 2005).

Following birth, the skin temperature of the newborn rises after an initial fall (Adamson and Towell 1965). This rise is mainly due to an increased heat production by “non-shivering thermogenesis”, i.e. an increased metabolic activity in the brown adipose tissue (BAT) without a rise in physical activity (Rutter 2005, Rylander et al. 1972). Following CS birth, this metabolic activity is not triggered (Vogl et al. 2006).

If the baby is put in skin-to-skin contact with the mother, a further rise of the infant’s skin temperature is observed. Warmth and touch received from the mother activate sensory nerves, which leads to a decrease in sympathetic tone and thereby, vasodilatation in the skin is induced and consequently results in a higher skin temperature (Bystrova et al. 2003). Oxytocin released from nerves in the NTS and other areas involved in cardiovascular control may contribute to this effect (Buijs et al. 1983, Sofroniew 1983).

After birth, maternal skin temperature starts to rise and to pulse, when mother and baby are in skin-to-skin contact (Bystrova et al. 2007a, Kimura and Matsuoka 2007) and the mother may experience “flushes” during breastfeeding (Marshall et al. 1992). In animal experiments, circulating oxytocin has been demonstrated to dilate cutaneous blood vessels in the skin overlying the mammary glands and thereby warmth is generated. Oxytocin acts by releasing the peptides calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP) from blood vessels (Eriksson et al. 1996, Uvnäs-Moberg and Eriksson 1996).

## **LONG-TERM EFFECTS INDUCED IN EARLY LIFE**

### *Effects in animals*

Long-term effects of increased interaction between mother and young during the first week of life have been demonstrated in animals. Pups born to rats that extensively licked and groomed their young have been shown to be less fearful in novel situations and show higher stress tolerance when compared to pups of low licking and grooming mothers. This higher tolerance to stress is reflected by lower levels of ACTH and corticosterone and increased expression of glucocorticoid receptors in the hippocampus

(Francis et al. 1999). In addition, rats having received extra sensory stimulation as pups raised their offspring in a similar way, i.e. by high licking and grooming. Furthermore, their decreased fear and increased social interaction are related to an increased amount and function of oxytocin receptors in the amygdala (Francis et al. 2002). In addition, these rats raised their own offspring by high licking and grooming. Taken together, these studies show that the type of maternal care can influence the level of social interaction and stress reactivity in the offspring and that these patterns of maternal behaviour can be transferred from one generation to the next (Francis et al. 1999). Such effects have been attributed to epigenetic phenomena (i.e. the activation and deactivation of certain genes in response to environmental stimuli) (Szyf et al. 2008).

Oxytocin administered in the early postnatal period, influenced interactive behaviour, decreased corticosterone levels and blood pressure and increased pain thresholds and body weight in the adult rat (Holst et al. 2002, Sohlström et al. 2000, Uvnäs-Moberg et al. 1998c). Whether these effects are also due to epigenetic phenomena is unknown.

#### *Effects in humans*

Klaus and co-workers (1972) coined the term “early sensitive period” and showed that extra contact between the human mother and baby for one hour after birth results in increased mother and infant interaction in a long-term perspective. Subsequent studies have supported that postpartum skin-to-skin contact between mother and newborn, as well as early breastfeeding, had positive effects on mother-newborn interaction and on the duration of breastfeeding (de Chateau and Wiberg 1977a and b, de Chateau and Wiberg 1984, Widström et al. 1990). A recent study suggested that early suckling is the most important factor for breastfeeding (Bystrova et al. 2007b). Early skin-to-skin contact had also a significant positive influence on maternal sensitivity, on mother-infant interaction and the infant’s capacity to regulate stress one year after birth was increased (Bystrova et al. 2009).

## **INTERVENTIONS DURING LABOUR**

In many labour wards interventions are made during the childbirth process. If labour is considered to be prolonged, contractions are stimulated by administration of oxytocin, mostly given as an intravenous drip. Furthermore, pharmacological or non-pharmacological pain relief is often administered in connection with labour. Epidural

analgesia (EDA), which was introduced a few decades ago, is today a common type of pharmacological pain relief (National Board of Health and Welfare, 2008a).

Previous studies have demonstrated that administration of different kinds of pharmacological pain relief induces adverse effects on the newborn's breastfeeding behaviour (Nissen et al. 1997, Ransjö-Arvidson et al. 2001) and increases crying and interscapular skin temperature in the newborn (Ransjö-Arvidson et al. 2001). CS delays the first mother-infant contact and the initiation and duration of breastfeeding (Rowe-Murray and Fisher 2002). Furthermore, mothers having undergone a CS show fewer oxytocin pulses during a breastfeed two days postpartum than mothers who had a normal birth, suggesting that the mothers having undergone CS have a less developed type of oxytocin pattern (Nissen et al. 1996). In addition, their maternal psychological adaptations as assessed by the Karolinska Scales of Personality (KSP) were less prominent.

Considering the facts mentioned above, other types of medical interventions administered during labour might also attenuate physiological and behavioural adaptations in the mother and newborn. Therefore, we chose to investigate if administration of oxytocin and of EDA disrupts normal adaptations in mother and newborn.

### **Administration of oxytocin**

Oxytocin infusion has been used since the 1950s in labour wards to initiate and to augment labour, in cases of labour arrest and in the prevention of postpartum haemorrhage (Engström 1958, Holmes 1954). Since then, the number of mothers receiving this treatment has increased to 50% in primiparae at the clinic where the study was conducted.

#### *Adverse effects of oxytocin stimulation on obstetrical processes*

Administration of oxytocin is not without complication. Women requiring oxytocin stimulation during labour have significantly longer labour than women labouring normally (Bugg et al. 2006; Svärdby et al. 2007). It is generally accepted that prolonged labour increase the need for more efficient pain relief. One of the most common forms of pharmacological pain relief for labour today is EDA. It is further under debate whether the use of EDA itself brings forth prolonged labour and thus increases the need

for exogenous oxytocin administration or whether it cuts pain during long and intolerable labours (Bugg et al. 2006, Sadler et al. 2000). Thus, the use of oxytocin and EDA are intertwined, and to separate effects on obstetric outcome is difficult.

Women with oxytocin stimulation during labour are also likely to have significantly more instrumental deliveries (i.e. CS, forceps, and ventouse deliveries) than women with normal labour (Bugg et al. 2006; Svärdby et al. 2007). Furthermore, oxytocin administered during labour may lead to hyperstimulation of the uterus and adverse consequences for the baby (Berglund et al. 2008, Jonsson et al. 2007). Oxytocin stimulation during the second stage of labour may cause lower pH and base excess in the umbilical cord blood at birth (Svärdby et al. 2007). The rates of perineotomies during augmentation with oxytocin showed an increase, especially in the group of women augmented during the second stage (Röckner 1991, Svärdby et al. 2007). Some authors have found that the number of women developing fever during labour is higher in women with augmented labour than in women without augmentation (Bugg et al. 2006). Oxytocin administration during labour has been shown to be followed by an increased foetal temperature *in utero* (Beck et al. 1979).

#### *Prophylactic use of oxytocin postpartum*

According to Swedish consensus all women should receive 8.3 µg (10 IU) oxytocin (Syntocinon®, Novartis, Täby, Sweden) intramuscularly after a vaginal birth in order to prevent postpartum haemorrhage (Nordström and Waldenström 2001). Bolus oxytocin infusions, when rapidly administered, have been studied in connection with CS and have been shown to influence the cardiovascular system inducing tachycardia and hypotension (Svanström et al. 2008, Thomas et al. 2007).

### **Epidural analgesia**

Epidural analgesia (EDA) is a pharmacological technique for pain relief used in Swedish labour wards. EDA can alleviate pain originating from the paracervical region, the pelvic and the superior hypogastric plexus during the first and second stage of labour (Eltzschig et al. 2003).

In 1973, 3% of all primiparae received EDA during labour in Stockholm, Sweden. The use of EDA has increased since then. In 2002 and 2003, when the present study was

conducted, 49% and 51%, respectively, of all primiparae received EDA for pain relief (National Board of Health and Welfare 2008b).

Throughout the time period that EDA has been used, possible side effects on the mother and infant have been discussed. In the past years, three systematic reviews have been published about the effects of EDA (Anim-Somuah et al. 2005, Leighton and Halpern 2002, Lieberman and O'Donoghue 2002). All three reviews concluded that the second stage of labour is prolonged in women having an EDA. However, there was no evidence that EDA caused an increased risk of instrumental delivery or CS (Anim-Somuah et al. 2005, Leighton and Halpern 2002, Lieberman and O'Donoghue 2002). Another well-known effect after EDA administration is hypotension (Anim-Somuah et al. 2005, Leighton and Halpern 2002). The hypotension is due to a rapid blockade caused by the local anaesthetic component of the EDA of the peripheral sympathetic nervous system, which results in vascular dilatations in the pelvis and the lower limbs (Brownridge and Cohen 1988).

EDA administration during labour may influence the temperature of the mother and her newborn. A rise (0.14 °C per hour) in maternal temperature was observed within the first hours following EDA (Fusi et al. 1989). Maternal fever was also observed during labour after EDA administration (D'Angelo et al. 1994, Lieberman and O'Donoghue 2002, Vinson et al. 1993). Another study reported an increase in the temperature both of the foetus *in utero* and the newborn, in connection with EDA (Macaulay et al. 1992).

Administration of EDA commonly leads to oxytocin stimulation at any stage of labour since EDA may attenuate uterine activity (Anim-Somuah et al. 2005; Leighton and Halpern 2002). This may be due to the fact that EDA may cause lower circulating oxytocin levels (Goodfellow et al. 1983, Rahm et al. 2002, Stocche et al. 2001). However, a decrease in circulating oxytocin was not confirmed by other authors (de Geest et al. 1985, Scull et al. 1998).

Published reports are inconclusive regarding the effects of EDA on breast-feeding duration and difficulties around breastfeeding. Wiklund et al. (2007) found that newborns were less likely to breastfeed within the first four hours of life when the mother was exposed to EDA. Further studies have shown that women who received EDA breastfeed for a shorter time than women not having had an EDA (Beilin et al.



2005, Henderson et al. 2003, Torvaldsen et al. 2006). In contrast, Chang and Heaman (2005) and Radzimirsky (2003) found no influence of EDA on breastfeeding performance.

In light of the historical findings described here, we were challenged to study whether different labour ward practices commonly used during and after labour, such as the administration of exogenous oxytocin and EDA, could influence the mother's and newborn's postpartum adaptations during the proxy of breastfeeding two days after birth, as well as in the long-term. It is not known if or how maternal oxytocin and prolactin release, maternal blood pressure and personality profile of mothers are influenced by these practices. Neither is it known whether administration of oxytocin or EDA influence the newborn's skin temperature. The present study was undertaken to elucidate possible effects.

## **2 AIMS**

This thesis explores postpartum physiological and psychological adaptations of mother and newborn in the short- and long-term perspective. The thesis further explores the influence of labour ward interventions, such as administration of oxytocin and EDA on these adaptations.

### **Specific aims**

- To examine the maternal oxytocin and prolactin release pattern in association with breastfeeding two days postpartum and in relation to different labour ward interventions **(I)**.
- To investigate the pattern of maternal blood pressure in response to breastfeeding two days postpartum and to study maternal blood pressure before and after breastfeeding during a six-month follow up period **(II)**.
- To study the personality profile of mothers two days postpartum in comparison to a reference group of non-pregnant, non-lactating women of the same age **(III)**.
- To study the personality profiles of mothers who have been exposed to different labour ward interventions at two days, two months, and six months postpartum **(III)**.
- To investigate the pattern of skin temperature in newborns in connection to a breastfeed two days post partum and in relation to different labour ward interventions **(IV)**.

### **3 MATERIAL AND METHODS**

#### **Setting**

This explorative and longitudinal study was conducted at one of the six labour wards in Stockholm, Sweden, from January 2002 to December 2003. This particular labour ward has approximately 2,500 deliveries per year, and only women who are expected to go through a normal childbirth (WHO 1996) are admitted. The ward has 14 delivery rooms and 14 postnatal family rooms designed to create an at-home feeling. All newborns are placed in skin-to-skin contact on their mother's chest after birth and stay in this position until the first breastfeed is established or until the newborn falls asleep. Further, breastfeeding on demand and day- and night rooming-in after birth are practised and mother-friendly care is strongly promoted (WHO 1989, WHO and Unicef 2009). During the first week postpartum, approximately 98% of all mothers breastfeed their newborn and at six months, 70 % of all mothers either partially or fully breastfeed (National Board of Health and Welfare 2008b). Exclusive breastfeeding during the first six months of life is globally recommended (WHO 2001).

#### **Inclusion criteria**

Mothers fulfilling the inclusion criteria (healthy, non-smoking, full-term, Swedish-speaking primiparae with a body mass index below 30) were informed about the aims and design of the study. The women should have had an uncomplicated singleton pregnancy and a normal birth with the infant born in vertex presentation. The child should have had an Apgar score of 8 or more at one minute postpartum, and a score of 9 at five minutes. Mother and infant should not have been separated after birth, not even for medical examinations. The newborns should have been exclusively breastfed on demand without receiving any formula. During the study periods, the mother-newborn dyads were consecutively recruited between Monday through Friday by one of two research midwives when the newborn was between 10 and 24 hours of age.

#### **Study groups**

The mothers had received different labour ward interventions: intravenous oxytocin stimulation during labour (OT iv group); 8.3 µg (10 IU) oxytocin intramuscularly after birth but no other treatment (OT im group); EDA with or without concomitant intravenous oxytocin stimulation during labour (EDA group); and no form of oxytocin (for augmentation of labour or as prophylaxis postpartum) or EDA during labour

(control group). In total, 86 mother-infant dyads were recruited for participation, and 72 participated in the study.

#### *Eligible non-participants*

Fourteen mothers declined to participate due to fatigue, wanting to be alone with their family, or without giving a reason. These mothers allowed the researchers access to their obstetric records. They showed no differences in the clinical background variables (maternal age, duration of pregnancy, duration of 1<sup>st</sup> and 2<sup>nd</sup> stages of labour, and neonatal birth weight) in comparison to the participating mothers. Of these fourteen mothers, ten had received EDA during labour; two had received oxytocin iv during labour, and two had not been exposed to any intervention.

#### *Number of participants in each sub-study*

The number of participants differed in the four sub-studies. The EDA group was divided into two groups: mothers who received EDA with exogenous oxytocin infusion (EDA<sup>OT</sup> group), and mothers who received EDA without concomitant oxytocin infusion (EDA<sup>non-OT</sup> group) (I). For further information, see Table 2.

**Table 2.** Number of participants in each sub-study.

Paper	Total n (n=72)	Control group (n=23)	OT iv group (n=10)	OT im group (n=15)	EDA group (with / without OT) (n=24)
I	61	20	8	13	20 (14/6)
II	66 (two days after birth) / 33 (during the 6-month follow up)				
III	69	22	9	15	23
IV	47	18	9	-	20

#### *Medical interventions during labour*

Labour started spontaneously in all mothers, but if inertia was diagnosed during labour oxytocin was administered intravenously. For that purpose, 8.3 µg (10 IU) oxytocin (Syntocinon<sup>®</sup>; Novartis, Täby, Sweden) were dissolved in 500 ml of Ringer's acetate solution (Fresenius Kabi AB, Uppsala, Sweden). If required, EDA was administered for pain relief. The pharmaceuticals most commonly used in Sweden for EDA are either

ropivacaine (Narop<sup>®</sup>, AstraZeneca, Södertälje, Sweden) or bupivacaine (Marcain<sup>®</sup>, AstraZeneca, Södertälje, Sweden), and the opioid Sufentanil (Sufenta<sup>®</sup>, Janssen-Cilag, Sollentuna, Sweden). According to Swedish guidelines for clinical practice, all women receive 8.3 µg (10 IU) oxytocin (Syntocinon<sup>®</sup>; Novartis AB, Täby, Sweden) intramuscularly to prevent postpartum haemorrhage. During the study period, midwives were instructed not to administer oxytocin intramuscularly to the women fulfilling the inclusion criteria. However, some midwives did not comply with this instruction and thereby some mothers *did* receive oxytocin intramuscularly postpartum. These mothers were included as a separate group (OT im group) in the study.

### **Procedure and data collection methods**

The mothers were told that the research midwives were going to be at the maternity ward the following morning and that the mother should call for them when the baby showed signs of wanting to breastfeed – for example, rooting behaviour (Prechtl 1958). The mothers were also advised to eat breakfast and to rest before the breastfeed. They were informed that participation was voluntary and that they could withdraw from the study without giving a reason, and that withdrawing would not influence the care they received. Mothers who gave their signed informed consent were included.

The study was carried out in the morning in the room assigned to the family at the maternity ward. The mother was laying in her bed and the baby was dressed and laying beside her. One of the research midwives measured maternal basal blood pressure on the right wrist with a wrist blood pressure monitor. Thereafter an intracubital vein catheter was inserted in the mother's right arm. The other research midwife undressed the baby and attached a skin temperature electrode between the newborn's shoulder blades. When these procedures were completed, the baby was placed in skin-to-skin contact between the mother's breasts. To keep the baby warm, his or her legs and trunk were covered with a light blanket. The mother was told that the researchers would not interfere with spontaneous maternal-infant interaction and initiation of breastfeeding. If the mother needed help she could ask the researchers for assistance. The conversation was kept to a minimum during the breastfeed. Clinical characteristics of mothers and infants were collected from obstetric records.

## **Blood sampling for oxytocin and prolactin (I)**

Maternal blood samples were collected in previously prepared ice-chilled tubes containing Trasylol<sup>®</sup> 10,000 KIU/ml plasma and Heparin<sup>®</sup> 5000 IU/ml plasma. Each sample contained approximately 3 ml blood.

The first blood sample was taken when the baby made the first suckling movements (sample 0). The next samples were drawn at 30-second intervals during the first 7.5 minutes. Thereafter the blood samples were drawn 10, 20, 30, and 60 minutes after suckling had begun. If breastfeeding finished before 60 minutes had passed, the mother was asked to keep her baby skin-to-skin on her chest until the last samples were collected. After 60 minutes, the mother's intracubital catheter was removed. After the breastfeed, the blood samples were centrifuged at +4°C, the plasma was taken off and the samples were stored at -20°C. The sampling method has been used by Nissen et al. (1996).

### *Chemical Analysis of oxytocin and prolactin*

Analysis of blood samples was performed by ELISA. Oxytocin levels were determined using the Correlate-EIA<sup>™</sup> Oxytocin Enzyme Immunoassay Kit according to manufacturer's instructions (Assay Designs, Inc., Ann Arbor, MI, USA). The amounts of prolactin were determined using the DSL-10-4500 ACTIVE<sup>®</sup> Prolactin Enzyme-Linked Immunosorbent Assay kit according to manufacturer's instructions (Diagnostic Systems Laboratories, Inc., Webster, TX, USA). Included on each plate were standards and controls as recommended by the manufacturer. Oxytocin and prolactin samples were diluted five times in assay buffer before analysis. The washing procedure was performed using an Anthos fluido microplate washer (Anthos Labtec Instruments GmbH CITY), and the absorbance was read using a Multiscan Ex microplate photometer (Thermo Electron Corporation CITY). The colour development of the samples was read at 405 nm for Oxytocin and at 450 nm for prolactin, with background correction at 620 nm for all samples. The Ascent software was used for creation of standard curves, curve fitting, and calculation of concentrations (Ascent, version 2.6 for iEMS Reader MF and Multiscan).

## **Maternal blood pressure measurements (II)**

Blood pressure was measured with a blood pressure monitor (Omron R5-1 Wrist blood pressure monitor, Omron Healthcare, Netherlands). For the follow-up study, mothers received a blood pressure monitor and instructions on how to use it.

### *Measurements of blood pressure two days postpartum*

Maternal blood pressure was measured after an initial resting period of at least 10 minutes in the supine position and approximately five minutes before the infant was put in the skin-to-skin position between the mother's breasts (basal blood pressure). Additionally, blood pressure was measured 10, 30, and 60 minutes after breastfeeding began.

### *Measurements of blood pressure during the follow-up study*

A sub-sample of 33 mothers participated in a follow-up study that lasted 25 weeks postpartum. These mothers were instructed to measure blood pressure at home once a week in the morning. They were advised to rest for ten minutes before taking their blood pressure and before breastfeeding their baby. When they finished breastfeeding, they measured their blood pressure again. The mothers were asked to record their blood pressure measurements in a diary protocol. Every third week during the 25-week follow-up periods, the research team contacted the mothers by telephone. They asked the mothers for the blood pressure measurements and the breastfeeding status.

## **Assessment of maternal personality pattern (III)**

All mothers were asked to fill in the KSP on three occasions: at day two after the breastfeed was finished and at two and six months postpartum.

The KSP is a personality inventory, which was developed by Daisy Schalling and collaborators (af Klinteberg et al. 1986). The scale has 135 items in a 4-point response format ranging from 1 (agree completely) to 4 (do not agree at all). It consists of 15 self-reported scales that can be divided into 4 main groups measuring different aspects of personality (Gustavsson 1997a).

The *Anxiety proneness scales* are composed of five subscales: *somatic anxiety* (autonomous disturbances such as rapid heartbeat and sweating), *psychic anxiety* (worrying and feeling socially insecure), *muscular tension* (difficulty relaxing),

*inhibition of aggression* (inability to speak up for oneself), and the *psychasthenia scale* (low mental energy and difficulty recovering from stress). The ***Extroversion related scales*** consist of three subscales for *impulsivity* (non-planning and acting on the spur of the moment), *monotony avoidance* (avoiding routine and seeking excitement), and *detachment* (need for distance in interpersonal relations). The ***Socialisation scale*** measures positive childhood experience and satisfaction with present life. The ***Social desirability scale*** measures social conformity. The five ***Aggression-hostility related scales*** measure *indirect aggression* (slamming doors), *verbal aggression* (shouting, arguing, or being overcritical), *irritability* (impatience or proneness to anger), *suspicion* (distrustfulness or projecting hostility onto others), and *guilt* (feeling remorseful or ashamed).

The KSP subscores are standardised for age and sex and are transformed to t-scores with a mean (m) of 50 and a standard deviation (sd) of 10. Mean scores deviating more than 5 (sd=10) from the normative sample were considered to be significant ( $p \leq 0.05$ ). The KSP is based on a sample of 200 non-pregnant or lactating randomly selected women referred to as the normative sample (af Klinteberg et al. 1986).

High scores on all scales indicate more problems, except for the socialisation and social desirability scales, where high scores indicate fewer problems.

The scale has been tested for more than two decades, is well established in Sweden, has high validity and test-retest stability (af Klinteberg et al. 1986, Gustavsson et al. 1997b). It has been used in several studies examining personality changes during pregnancy and lactation (Nissen et al. 1998, Ryding et al. 2007, Sjögren et al. 2000, Sjögren et al. 2004, Uvnäs-Moberg et al. 1990b, Wiklund et al. 2006).

#### **Newborn skin temperature (IV)**

A portable electronic thermometer (Ellab, Copenhagen, Denmark) with an accuracy of  $\pm 0.1^\circ\text{C}$  was used to measure newborn skin temperature. The thermometer had a sensor with a diameter of 5 mm that was attached (using skin-friendly tape) to the infant's back between the shoulder blades. When the infant was put skin-to-skin on the chest of the mother, the infant's interscapular temperature was measured immediately and also



measured 5, 10, 20, and 30 minutes after the newborn was placed in the skin-to-skin position.

#### *Environmental temperature*

The air temperature in the family room varied between 22.4 to 24.0°C.

#### **Breastfeeding variables (I, II, III, and IV)**

Information about how often the infant breastfed since birth was collected from the mothers. The duration of skin-to-skin contact before the baby initiated breastfeeding and the duration of the breastfeed two days postpartum was recorded in the study protocol. The 33 mothers who participated in the 25-week follow-up study (Paper II) were asked if they were breastfeeding exclusively or partially.

#### **Statistical analysis**

The statistics were computed using the Statistical Package for the Social Sciences (SPSS, versions 12.0 - 14.0). Clinical background data were described by medians and percentiles ( $Q_{25}$ - $Q_{75}$ ) in Papers I-IV. For testing differences in background data between groups, the Kruskal-Wallis test for independent samples, the Mann-Whitney U test, and Chi-square tests were performed (**I, IV**). To calculate differences between and within groups in temperature and blood pressure paired and unpaired t-tests were performed (**II, IV**). In order to test relationships between background data and hormonal levels and background data and temperature, the Spearman rank correlation coefficient ( $r_s$ ) and Pearson's correlation coefficient ( $r$ ), respectively, were calculated (**I, IV**). For testing differences in hormonal levels within groups over time, the Wilcoxon signed-rank test was used (**I**). ANOVA for repeated measurements with contrasts was used for analysing the development of blood pressure over time (**II**). An ANCOVA was performed for testing differences in KSP scores between groups and impact of co-variates (**III**). An exploratory multiple regression analysis was performed to study the impact of background variables on temperature (**IV**). The significance level was set at  $p \leq 0.05$ .

#### **Ethical considerations**

The Ethics Committee at the Karolinska Hospital in Stockholm, Sweden, approved the studies. All mothers had given their written informed consent.

Most of the data were collected two days after birth when mothers and their newborns were in a period of getting to know each other and establish breastfeeding. We were aware that the methods of our study could disturb mother and baby while breastfeeding. It might seem quite invasive to insert an intracubital vein catheter, since it might hurt or interfere with spontaneous maternal movements. In order to avoid even more disturbance, the researchers were as careful as possible with respect to draw blood samples and to measure blood pressure, for example. All data collection was performed by the same two experienced midwives in a very calm way. Conversation was kept to a minimum to allow undisturbed mother-infant interaction.

## **4 RESULTS**

This thesis explored some postpartum physiological and psychological adaptations of mother and newborn in the short- and long-term perspective. It was further explored, if and how exogenous oxytocin infusion and EDA administered during birth and intramuscular oxytocin injection administered postpartum influence maternal and infant adaptations. Four different outcomes were studied. The first outcome was the mothers' own hormone profile with respect to release of oxytocin and prolactin in connection with breastfeeding two days postpartum (**I**). The second outcome was the maternal blood pressure pattern in connection with breastfeeding two days after birth and during the first six months postpartum (**II**). The third outcome was the personality profile as measured by the Karolinska Scales of Personality (KSP) in breastfeeding women two days and at 2 and 6 months after childbirth (**III**). The fourth outcome was the newborn's interscapular temperature pattern in connection with breastfeeding two days postpartum (**IV**).

In the following section, only the most important results will be briefly presented. For a detailed description, reference is made to the original article (**I-IV**).

### **Clinical and pharmacological background data**

All mothers except one were cohabiting with the newborn's father. Seventy-five percent of all mothers had a university degree and lived in an area with good socio-economic status. None of the mothers smoked. Detailed background information is presented in Table 3. Pharmacological background data as to the medical interventions administered to the mothers during labour are presented in Table 4.

### **Oxytocin and prolactin release in response to breastfeeding (I)**

The release of maternal oxytocin and prolactin were determined in association with breastfeeding two days postpartum in the whole group of women and in relation to different labour ward routines.

The first blood sample was drawn immediately after the baby had started to suckle the breast (sample 0). The next samples followed at 30-second intervals during the first 7.5 minutes. After that the blood samples were collected at 10, 20, 30, and 60 minutes after breastfeeding had started.

**Table 3.** Clinical background data of all participating mothers and their newborns (n=72). Data are presented as medians and interquartile distances (Q<sub>25</sub> - Q<sub>75</sub>).\*

	Control group (n=23) Median (Q <sub>25</sub> - Q <sub>75</sub> )	OT iv group (n=10) Median (Q <sub>25</sub> - Q <sub>75</sub> )	OT im group (n=15) Median (Q <sub>25</sub> - Q <sub>75</sub> )	EDA group (n=24) Median (Q <sub>25</sub> - Q <sub>75</sub> )
Maternal age	31 (28-33)	31 (29-33)	28 (27-29)	31 (29-34)
Pregnancy (wks)	40 (39-41)	40 (39-40)	40 (39-40)	40 (39-40)
Duration of 1 <sup>st</sup> + 2 <sup>nd</sup> stage of labour (hrs:mins)	7:39 (6-10:46)	10:49 (9:54-13:17)	9:49 (6:20-12:41)	11:58 (8:28-13:49)
Postpartum bleeding (ml)	400 (300-500)	375 (275-775)	450 (300-850)	490 (312-637)
Birth weight (gr)	3525 (3190-3675)	4047 (3323-4240)	3745 (3370-4090)	3582 (3345-3761)
Neonatal age (hrs) at experiment	36 (26-39)	36 (34-38)	26 (23-40)	33 (27-40)
Number of breastfeeding since birth	8 (7-10)	6 (4.5-10.5)	5 (4-9)	6 (5-8)
Duration of skin-to-skin contact between mother and newborn before breastfeeding (mins)	2 (1-9)	2:30 (1-11:15)	2 (1-6)	3 (1-6)
Duration of breastfeeding (mins)	27 (19-35)	22 (15.5-39.5)	35 (20-42)	22 (12-30)

\*Significant differences between groups in *Maternal age* (p=0.014) and *Neonatal weight* (p=0.023) were found using the Kruskal Wallis test.

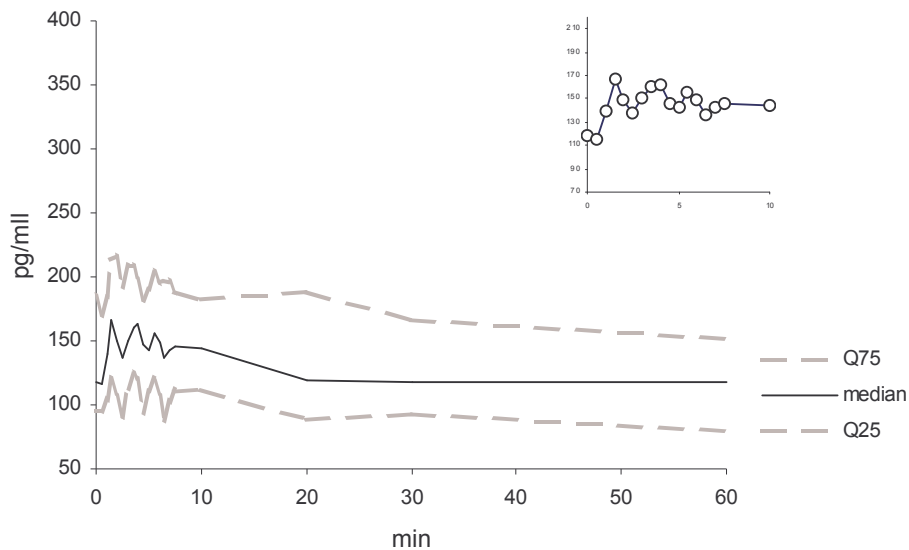
**Table 4.** The table presents pharmacological background data as to the medical interventions administered to the mothers during labour. Medians and interquartile distances (Q<sub>25</sub>- Q<sub>75</sub>) are presented. Minimum/maximum amounts of Bupivacaine, Sufentanil and Oxytocin, administered are given in brackets [ . ] .

	OT iv group (n=10) Median (Q <sub>25</sub> - Q <sub>75</sub> )	EDA <sup>01</sup> group (n=17) Median (Q <sub>25</sub> - Q <sub>75</sub> )	EDA <sup>non-01</sup> group (n=7) Median (Q <sub>25</sub> - Q <sub>75</sub> )
EDA:			
Duration of EDA infusion (hrs:mins)		4:53 (3:05-7:28)	4:09 (2:27-4:58)
Amount of Bupivacaine (mg)		17.5 (17.5-42.5) [17.5-52.5]	22.5 (17.5-27.5) [12.5-57.5]
Amount of Sufentanil (µg)		10 (10-35) [10-45]	10 (10-20) [10-50]
Oxytocin infusion:			
Amount of oxytocin infusion (ml) (500 ml Ringer's acetate + 8.3 µg/10 IU oxytocin	93.50 (36.75-147) [20-185]	120 (58-199) [86-500]	
Amount of oxytocin (µg)	1.55 (0.61-2.44) [0.33-3.07]	1.59 (0.83-2.82) [0.48-8.3]	

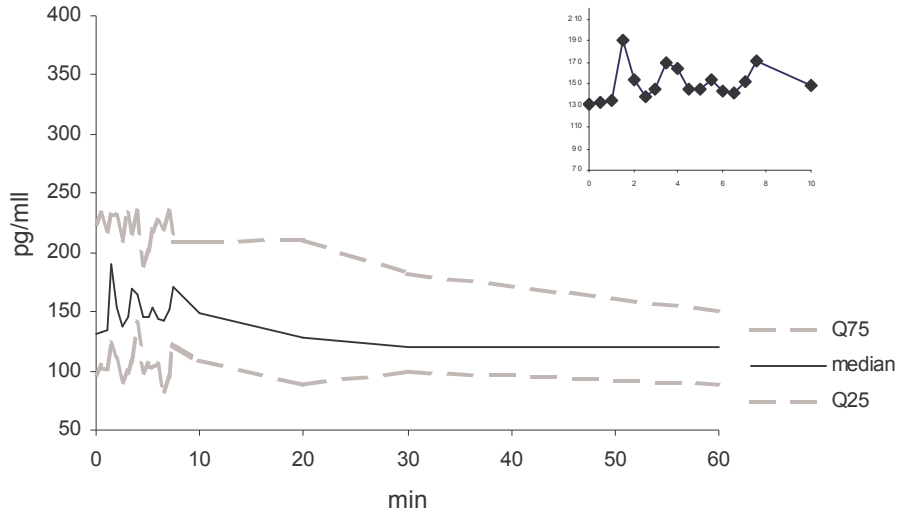
### Oxytocin

The median (lower and upper quartiles (Q<sub>25</sub>-Q<sub>75</sub>)) oxytocin level at the start of suckling for the entire group of women was 119.7 (96.4-217.5) pg/ml. The median (Q<sub>25</sub>-Q<sub>75</sub>) oxytocin levels increased significantly to 166.6 (119.7- 215.1) pg/ml within 90 seconds after start of suckling (p=0.001). During the first 7.5 minutes, a pulsatile oxytocin pattern was recorded. Three to four pulses were visually observed during this time period (Figure 1a).

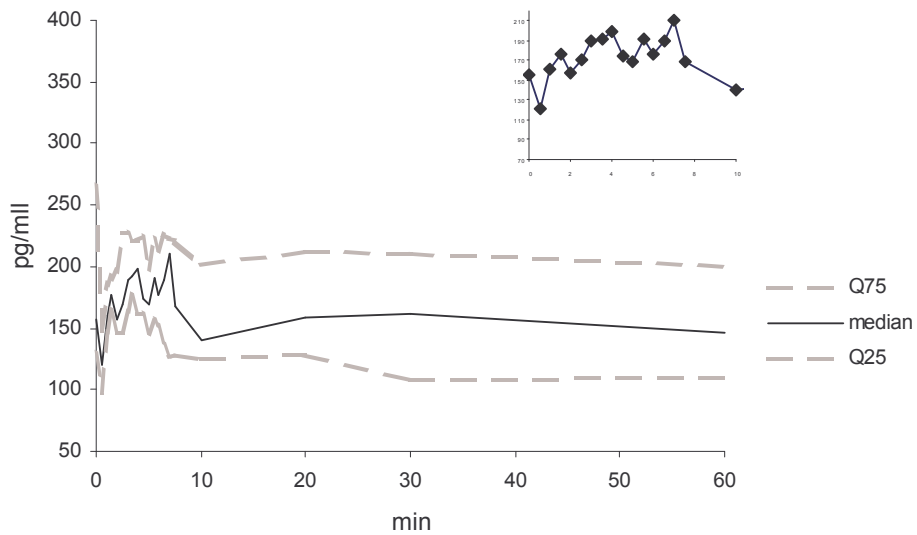
The median oxytocin level was lower in the EDA<sup>OT</sup> group in comparison to the other treatment groups (OT iv group, p=0.005, OT im group, p=0.033 and EDA<sup>non-OT</sup> group, p=0.051) (Figures 1b-1f). There was a significant negative correlation between the amount of exogenous oxytocin infused during labour and the mothers' endogenous median oxytocin levels two days after birth in the women who received oxytocin infusions during labour (OT iv group and EDA<sup>OT</sup> subgroup). In other words, the higher the dose of infused oxytocin during labour, the lower the women's endogenous oxytocin levels two days after birth ( $r_s = -0.495$ , p=0.019).



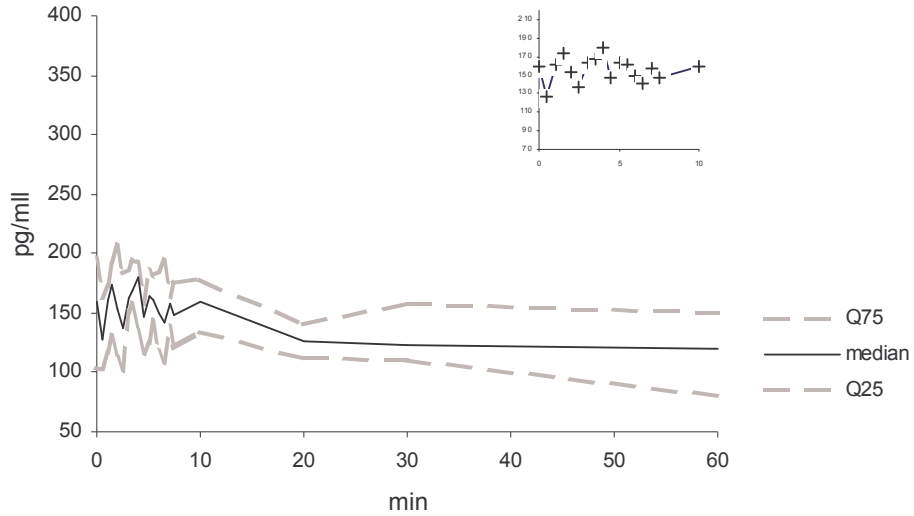
**Figure 1a.** Median and upper and lower quartiles (Q<sub>75</sub> and Q<sub>25</sub>) for oxytocin plasma levels (pg/ml) during a breastfeed two days postpartum for all participants (n=61). Blood samples were collected at start of suckling (0) and at 10, 20, 30, and 60 minutes after start of suckling. The box in the upper right corner presents a close-up of the first 7.5 minutes of breastfeeding, where blood samples were collected with 30-second intervals.



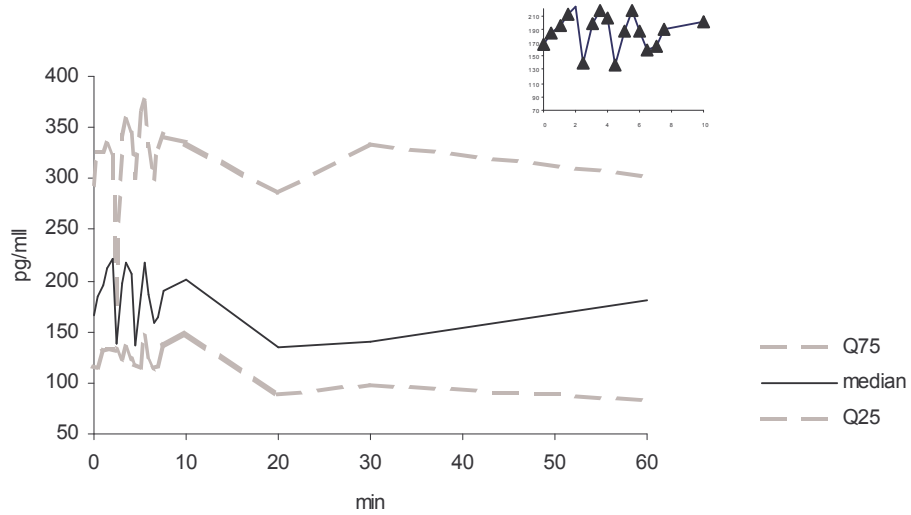
**Figure 1b.** Median and upper and lower quartiles (Q<sub>75</sub> and Q<sub>25</sub>) for oxytocin plasma levels (pg/ml) during a breastfeed two days postpartum for the control group (n=20). Blood samples were collected at start of suckling (0) and at 10, 20, 30, and 60 minutes after start of suckling. The box in the upper right corner presents a close-up of the first 7.5 minutes of breastfeeding, where blood samples were collected with 30-second intervals.



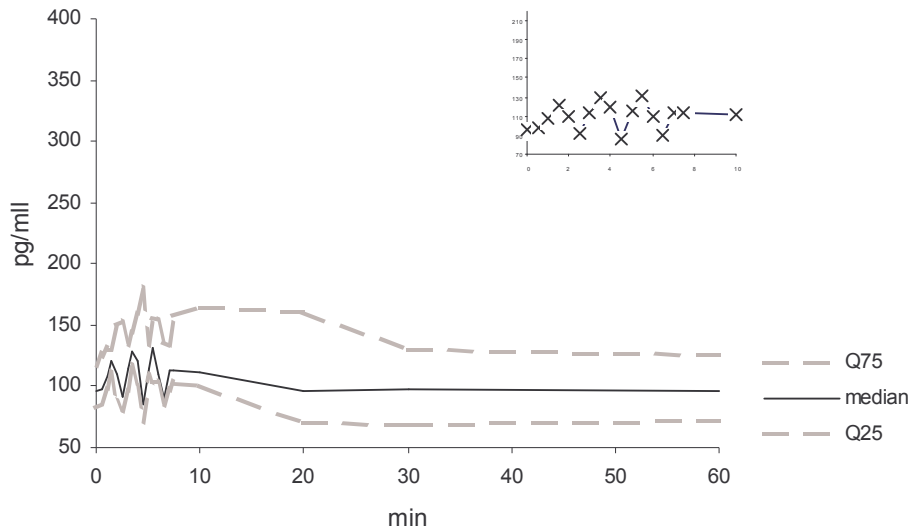
**Figure 1c.** Median and upper and lower quartiles (Q<sub>75</sub> and Q<sub>25</sub>) for oxytocin plasma levels (pg/ml) during a breastfeed two days postpartum for the OT iv group (n=8). Blood samples were collected at start of suckling (0) and at 10, 20, 30, and 60 minutes after start of suckling. The box in the upper right corner presents a close-up of the first 7.5 minutes of breastfeeding, where blood samples were collected with 30-second intervals.



**Figure 1d.** Median and upper and lower quartiles (Q<sub>75</sub> and Q<sub>25</sub>) for oxytocin plasma levels (pg/ml) during a breastfeed two days postpartum for the OT im group (n=13). Blood samples were collected at start of suckling (0) and at 10, 20, 30, and 60 minutes after start of suckling. The box in the upper right corner presents a close-up of the first 7.5 minutes of breastfeeding, where blood samples were collected with 30-second intervals.



**Figure 1e.** Median and upper and lower quartiles (Q<sub>75</sub> and Q<sub>25</sub>) for oxytocin plasma levels (pg/ml) during a breastfeed two days postpartum for the EDA<sup>non-OT</sup> group (n=6). Blood samples were collected at start of suckling (0) and at 10, 20, 30, and 60 minutes after start of suckling. The box in the upper right corner presents a close-up of the first 7.5 minutes of breastfeeding, where blood samples were collected



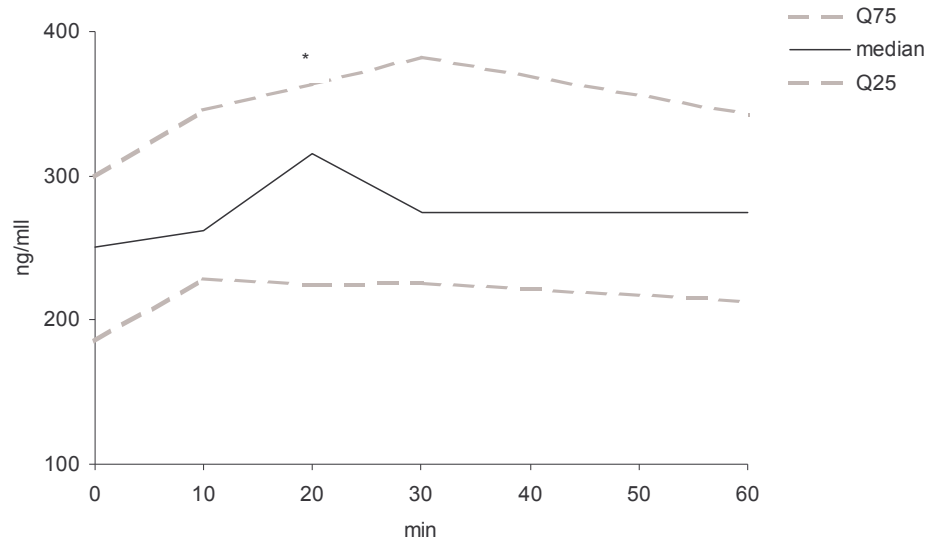
**Figure 1f.** Median and upper and lower quartiles (Q<sub>75</sub> and Q<sub>25</sub>) for oxytocin plasma levels (pg/ml) during a breastfeed two days postpartum for the EDA<sup>OT</sup> group (n=14). Blood samples were collected at start of suckling (0) and at 10, 20, 30, and 60 minutes after start of suckling. The box in the upper right corner presents a close-up of the first 7.5 minutes of breastfeeding, where blood samples were collected with 30-second intervals.

### *Prolactin*

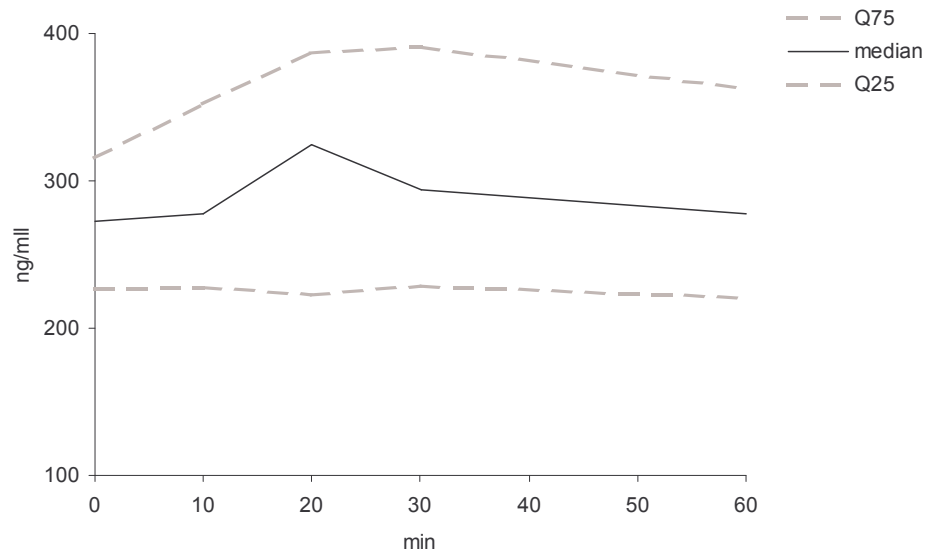
The median (lower and upper quartiles (Q<sub>25</sub>-Q<sub>75</sub>)) prolactin level for the entire group of women was 250.4 ng/ml (180.8-304.1). A significant rise of median (Q<sub>25</sub>-Q<sub>75</sub>) prolactin level to 315.4 (223.2-364.1) ng/ml was noted 20 minutes after suckling had begun (p≤0.0001) (Figure 2a).

When the different groups were analysed separately, a significant increase of median prolactin levels was observed after only ten minutes of breastfeeding in the OT iv and EDA<sup>OT</sup> groups (p=0.012 and p=0.008, respectively). This was not seen in the other groups. This increase in prolactin levels during the first ten minutes of breastfeeding in the OT iv and EDA<sup>OT</sup> groups differed significantly from the control group (p=0.006 and p=0.023, respectively). After 20 minutes of breastfeeding, the prolactin levels were significantly elevated in all groups except the EDA<sup>non-OT</sup> group. In the control group, the observed rise was, however not significant. Prolactin levels were still elevated in comparison to the start of breastfeeding in the OT iv and EDA<sup>OT</sup> groups (p=0.0012 and p=0.0023, respectively) after 60 minutes (Figures 2b-2f). This was not observed in the other groups.

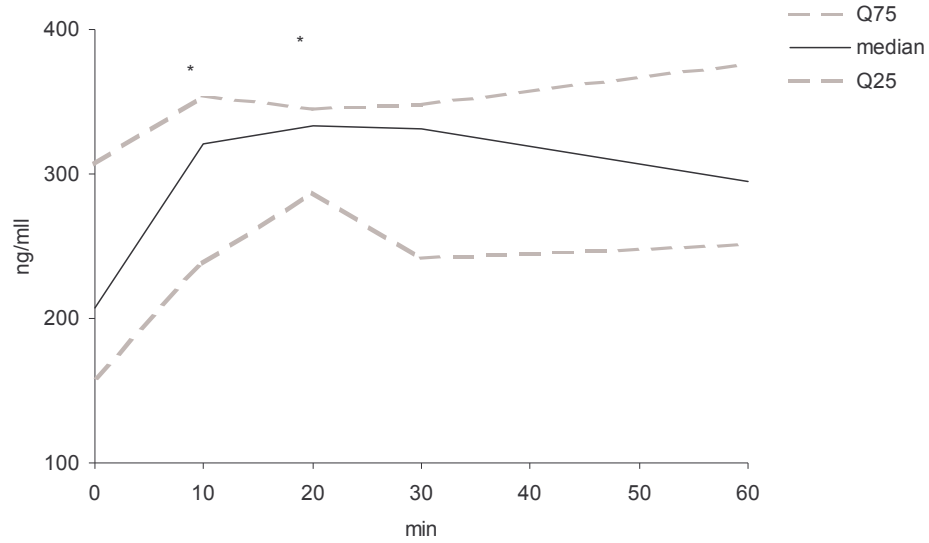




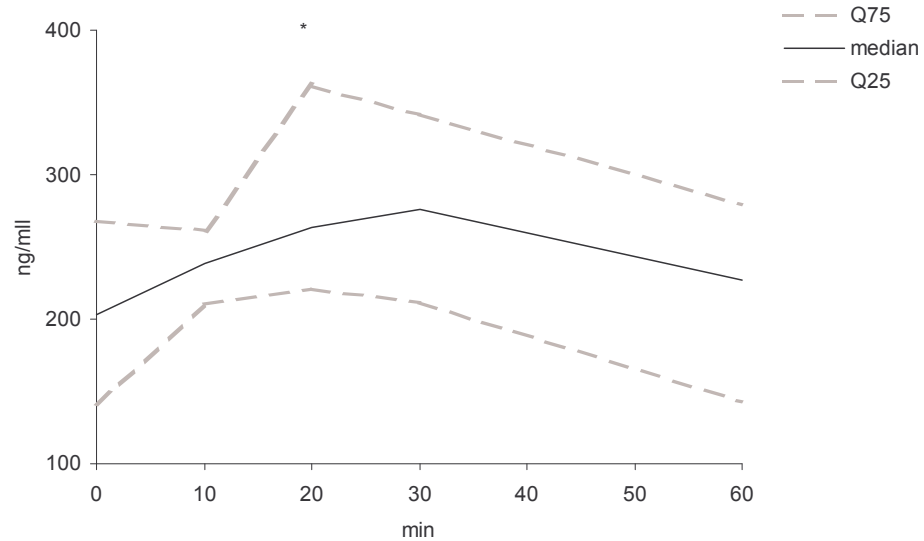
**Figure 2a.** Median and upper and lower quartiles (Q<sub>75</sub> and Q<sub>25</sub>) for prolactin plasma levels (ng/ml) during a breastfeed two days postpartum for all participants (n=61). Blood samples were collected at start of suckling (0) and at 10, 20, 30, and 60 minutes after start of suckling. A significant rise in prolactin levels is marked by an asterisk (\*).



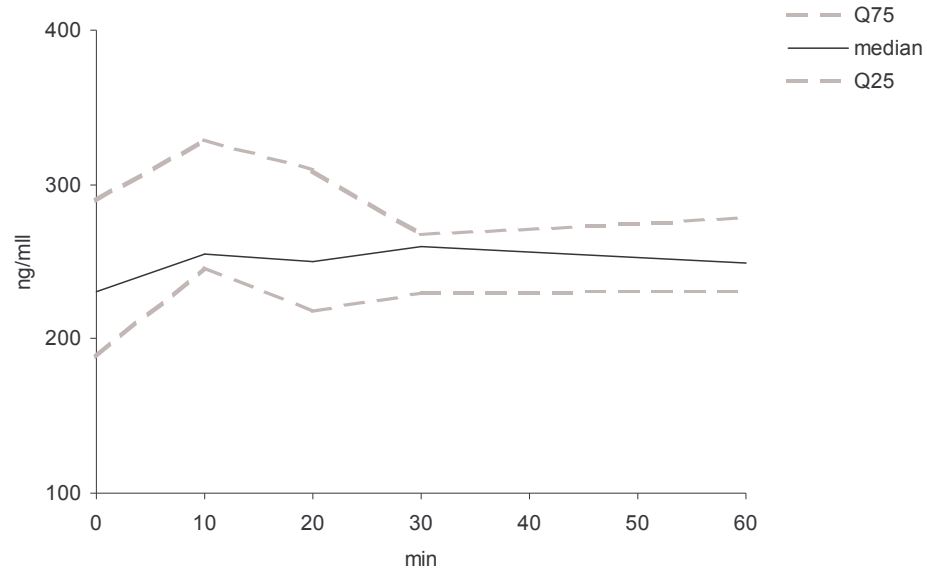
**Figure 2b.** Median and upper and lower quartiles (Q<sub>75</sub> and Q<sub>25</sub>) for prolactin plasma levels (ng/ml) during a breastfeed two days postpartum for the control group (n=20). Blood samples were collected at start of suckling (0) and at 10, 20, 30, and 60 minutes after start of suckling.



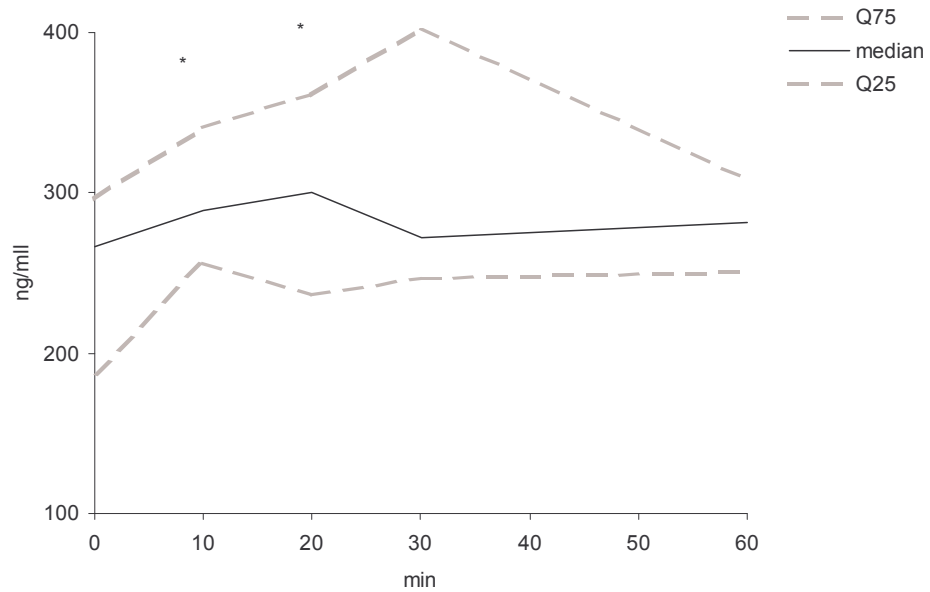
**Figure 2c.** Median and upper and lower quartiles (Q<sub>75</sub> and Q<sub>25</sub>) for prolactin plasma levels (ng/ml) during a breastfeed two days postpartum for the OT iv group (n=8). Blood samples were collected at start of suckling (0) and at 10, 20, 30, and 60 minutes after start of suckling. A significant rise in prolactin levels is marked by an asterisk (\*).



**Figure 2d.** Median and upper and lower quartiles (Q<sub>75</sub> and Q<sub>25</sub>) for prolactin plasma levels (ng/ml) during a breastfeed two days postpartum for the OT im group (n=13). Blood samples were collected at start of suckling (0) and at 10, 20, 30, and 60 minutes after start of suckling. A significant rise in prolactin levels is marked by an asterisk (\*).



**Figure 2e.** Median and upper and lower quartiles (Q<sub>75</sub> and Q<sub>25</sub>) for prolactin plasma levels (ng/ml) during a breastfeed two days postpartum for the EDA<sup>non-OT</sup> (n=6). Blood samples were collected at start of suckling (0) and at 10, 20, 30, and 60 minutes after start of suckling.



**Figure 2f.** Median and upper and lower quartiles (Q<sub>75</sub> and Q<sub>25</sub>) for prolactin plasma levels (ng/ml) during a breastfeed two days postpartum for the EDA<sup>OT</sup> (n=14). Blood samples were collected at start of suckling (0) and at 10, 20, 30, and 60 minutes after start of suckling. A significant rise in prolactin levels is marked by an asterisk (\*).

### *Relationship between duration of breastfeeding and prolactin release*

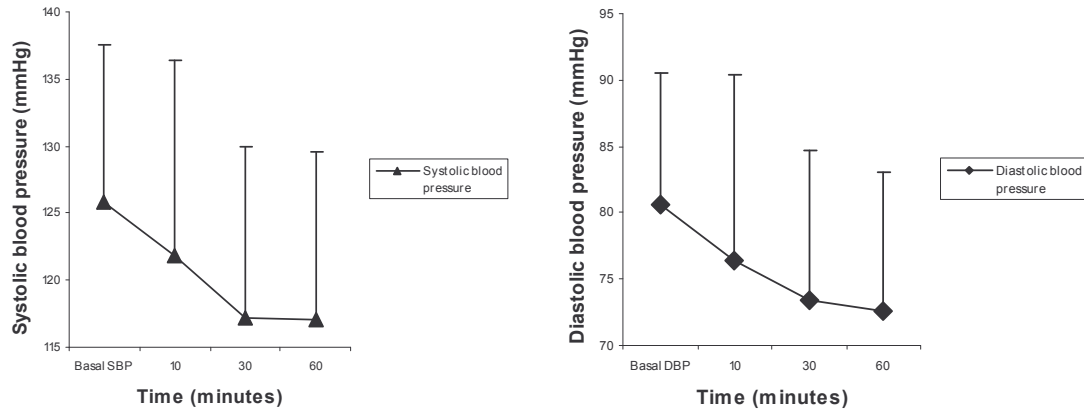
In all mothers, there was a significant positive correlation between the duration of the breastfeed and median prolactin levels ( $r_s=0.268$ ,  $p=0.040$ ).

### **Maternal blood pressure (II)**

Maternal blood pressure in response to breastfeeding two days postpartum and during a six-month follow-up period was investigated. Blood pressure was recorded approximately 5 minutes before skin-to-skin contact (basal blood pressure) and also 10, 30, and 60 minutes after onset of breastfeeding two days after birth.

### *Blood pressure during the breastfeeding experiment two days after birth*

The mean (standard deviation (sd)) systolic and diastolic blood pressure averaged 125.8 (sd=11.75) mmHg and 80.7 (sd=9.8) mmHg, respectively, at the start of the experiments; that is, approximately 5 minutes before skin-to-skin contact between mother and baby was established (Figures 3a and 3b). An analysis performed by ANOVA for repeated measurements showed a significant decrease in systolic and diastolic blood pressure over the 60-minute breastfeed ( $df=3$ ,  $F=19.929$ ,  $p<0.001$  and  $F=16.727$ ,  $p<0.001$ , respectively). The total fall in mean systolic and diastolic blood pressure during the entire breastfeed amounted to 8.8 (sd=11.0) and 7.7 (sd=9.3) mmHg, respectively. Furthermore, both systolic and diastolic blood pressure decreased significantly between each measurement during the breastfeeding experiment two days after birth. Both systolic ( $df=1$ ,  $F=5.772$ ,  $p=0.020$ ) and diastolic blood pressure ( $df=1$ ,  $F=8.005$ ,  $p=0.006$ ) fell significantly after only 10 minutes of suckling.



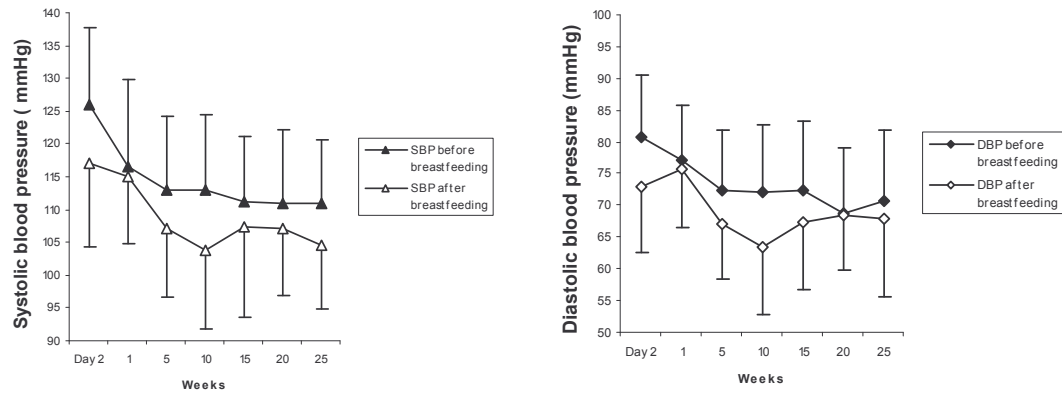
**Figures 3a and 3b.** The mean and standard deviation of systolic and diastolic blood pressure (SBP and DBP, respectively) (mmHg) recorded at five minutes before skin-to-skin contact between mother and newborn (basal BP) and at 0, 30, and 60 minutes after start of breastfeeding two days after birth (n=66).

#### *Long-term effects of breastfeeding on blood pressure*

Thirty-three mothers continued to measure blood pressure before and after breastfeeding in their homes for a period of 25 weeks. These mothers reported that they were breastfeeding exclusively. Nineteen of those mothers had complete series of blood pressure measurements. The 33 mothers asked to participate in the follow-up study did not differ significantly from the total group of 66 mothers participating in the experiment two days after birth in respect to maternal age, duration of pregnancy, duration of 1<sup>st</sup> and 2<sup>nd</sup> stages of labour, and neonatal birth weight.

Data for the systolic and diastolic blood pressure obtained before breastfeeding two days after birth and obtained 1, 10, and 25 weeks after birth showed that mothers' blood pressure decreased during the entire observation period. This fall was significant both for systolic (df=3, F=7.843, p<0.001) and for diastolic (df=3, F=5.453, p=0.002) blood pressure. It amounted to a mean of 15 (sd=10.4) mmHg and 10 (sd=9.7) mmHg, respectively (Figures 4a and 4b). Furthermore, systolic and diastolic blood pressure decreased significantly between weeks 1 and 10 (p=0.003 and p=0.022, respectively) and between weeks 10 and 25 (p=0.04 and p=0.020, respectively) (Figures 4a and 4b).

In addition, blood pressure continued to decrease significantly during most of the individual breastfeeding sessions during the 25-week follow-up (Figures 4a and 4b)



**Figures 4a and 4b.** The mean and standard deviation of systolic and diastolic blood pressure (SBP and DBP, respectively) (mmHg) recorded before (solid symbols) and after (open symbols) a breastfeed two days after birth and at 1, 5, 10, 15, 20, and 25 weeks after birth (n=23-66).

### Personality profile in breastfeeding women (III)

The personality profiles of the mothers on the second day postpartum were studied and compared to a normative sample of non-pregnant, non-lactating women of the same age.

#### *Mean KSP scores in the subgroups compared to the normative group*

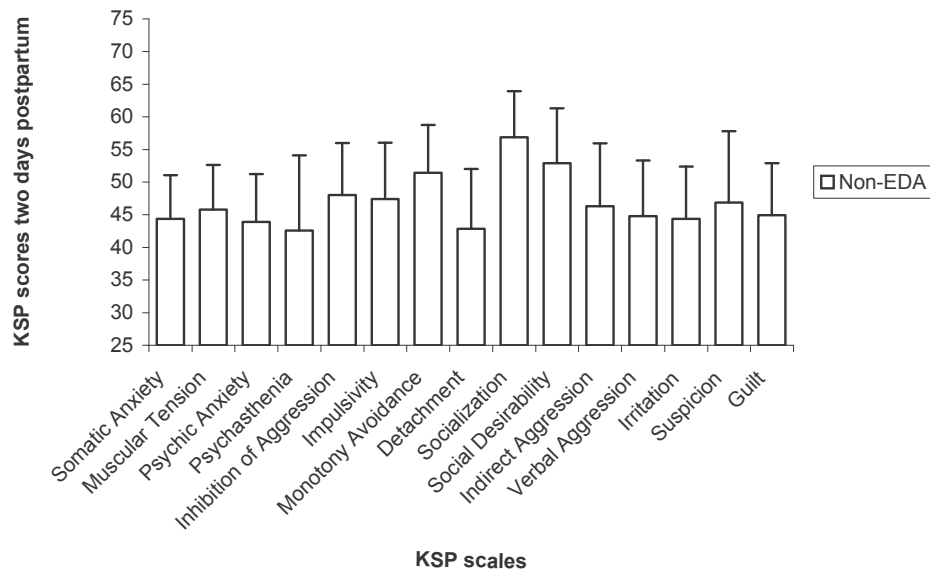
The unmedicated control group, the OT iv group, and the OT im group differed from the normative group of women two days after birth, and these differences were sustained throughout the entire study period. The scores related to *somatic* and *psychic anxiety* and *psychasthenia* were lower than in the normative group on day 2 and at two and six months after birth. The same groups had also higher scores for *socialisation* and lower scores for *detachment* in comparison to the normative group for all points in time. In addition, the aggression-hostility related scales were influenced. No such differences were found in the EDA group (Figures 5a and 5b).

#### *Differences in KSP scores between the EDA group and the other groups two days postpartum*

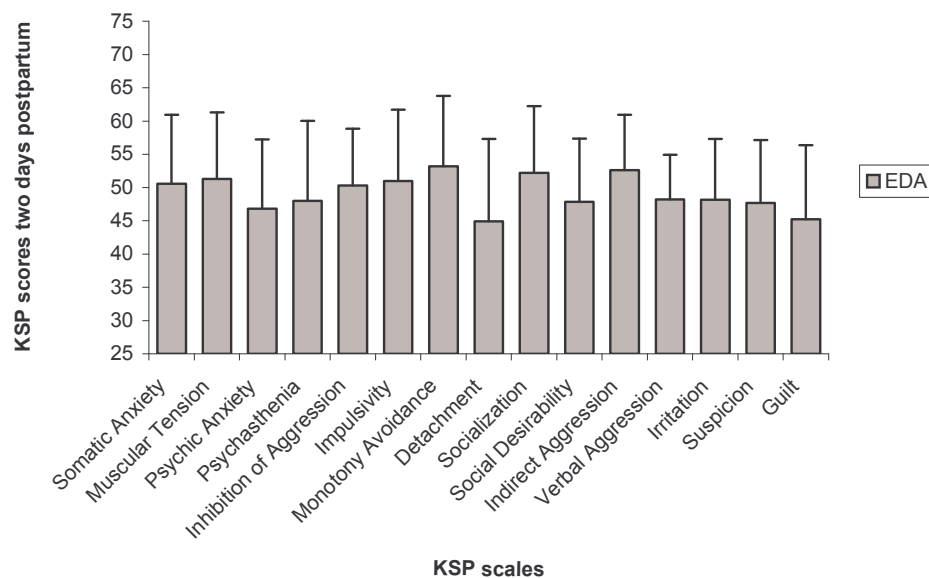
In order to test differences between treatments two days after birth, an analysis of covariance (ANCOVA) was performed. In this ANCOVA, EDA (not having an EDA = 0 / having an EDA = 1) and OT im (not receiving OT im = 0 / receiving OT im = 1) were used as factors. The amount of oxytocin infused (OT dose) was used as a covariate. The

dependent variables in the analysis of the data collected two days postpartum were the mean scores of the KSP subscales.

Mothers who had not received an EDA had lower scores than the mothers in the EDA group for the subscales *somatic anxiety* (95% CI 2.36; 12.46,  $p=0.005$ ), *muscular tension* (95% CI 1.18; 11.04,  $p=0.016$ ), *indirect aggression* (95%CI 1.06; 12.69,  $p=0.021$ ), and *irritability* (95% CI 0.89; 11.30,  $p=0.023$ ). Furthermore, the mothers who had not received an EDA had higher scores than the mothers in the EDA group for the subscale *social desirability* (95% CI -11.32; 0.13,  $p=0.045$ ) (Figure 5b). Thus, the KSP pattern of the EDA group resembled the KSP pattern of the mothers from the normative group. The OT dose significantly influenced the subscale *inhibition of aggression* (95% CI -0.05; -0.01,  $p=0.019$ ). Hence, the more oxytocin infused during birth, the lower the scores on this subscale.



**Figures 5a.** The KSP scores (mean and standard deviation) of the fifteen subscales obtained two days postpartum. White bars represent values of the mothers who did not receive EDA ( $n=44$ ). The y-axis starts with scores above 25.



**Figures 5b.** The KSP scores (mean and standard deviation) of the fifteen subscales obtained two days postpartum. Shaded bars represent values of the mothers belonging to the EDA group (n=19). The y-axis starts with scores above 25.

#### *Changes in the KSP scores two days versus two months postpartum*

To test differences between treatments over the two- and six-month study periods, two ANCOVAs were performed according to the previously presented model. The dependent variables used, however, were the calculated differences between the KSP mean scores obtained in the KSP subscales at two days and two months and at two days and six months postpartum.

When studying changes from two days to two months postpartum in the different subscales, the scores of the mothers who did not receive an EDA remained stable.

In the EDA group, though, a significant decrease over time in the following subscales appeared: *somatic anxiety* (95% CI -9.85; -2.33, p=0.002), *muscular tension* (95% CI -9.50; -1.87, p=0.004), *psychic anxiety* (95% CI -7.84; -1.31, p=0.007), and *psychasthenia* (95% CI -13.21; -4.17, p=<0.0001).

In addition, there was a decrease in the scores of the subscales *inhibition of aggression* and *detachment* (95% CI -11.39; -2.26, p=0.004 and 95% CI-8.22; -0.62, p=0.023,

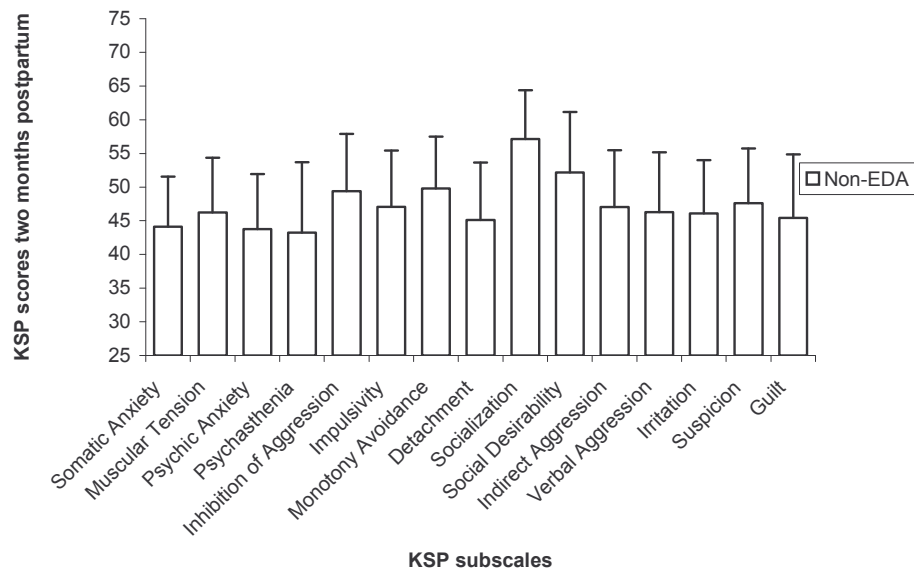


respectively), and the *socialisation* scores increased (95% CI 1.12; 7.26,  $p=0.008$ ). Thus, the EDA group had approached the scores of the other groups (Figures 6a and 6b).

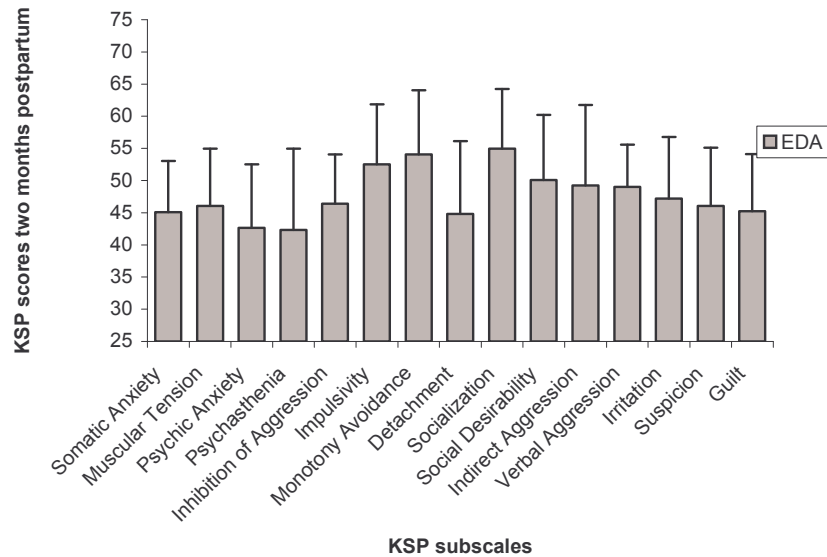
In addition, a significant effect of the OT dose infused during labour was also found on the scores of the *psychasthenia* scale: the more oxytocin infused during labour, the greater the fall in the scores of *psychasthenia* during this time period (95% CI -0.04; -0.01,  $p=0.028$ ).

#### *Changes in the KSP scores two days versus six months postpartum*

When changes from two days to six months postpartum were studied in the different subscales, the scores of the mothers who did not receive EDA remained stable. Hence, in mothers who received EDA, the scores for *somatic anxiety* (95% CI -6.84; -0.72,  $p=0.016$ ), *muscular tension* (95% CI -10.01; -2.28,  $p=0.002$ ), *psychasthenia* (95% CI -12.35; 0.51,  $p=0.034$ ), and *detachment* (95% CI -11.84; -1.39,  $p=0.014$ ) were decreased, whereas the score for *socialisation* was increased (95% CI 0.08; 6.76,  $p=0.045$ ). The more oxytocin infused during labour, the greater the fall of *muscular tension* between two days and six months postpartum 95% CI -0.04; 3.13,  $p=0.050$ ).



**Figure 6a.** The KSP scores (mean and standard deviation) of the fifteen subscales obtained two months postpartum. White bars represent values of the mothers who did not receive EDA ( $n=43$ ). The y-axis starts with scores above 25.



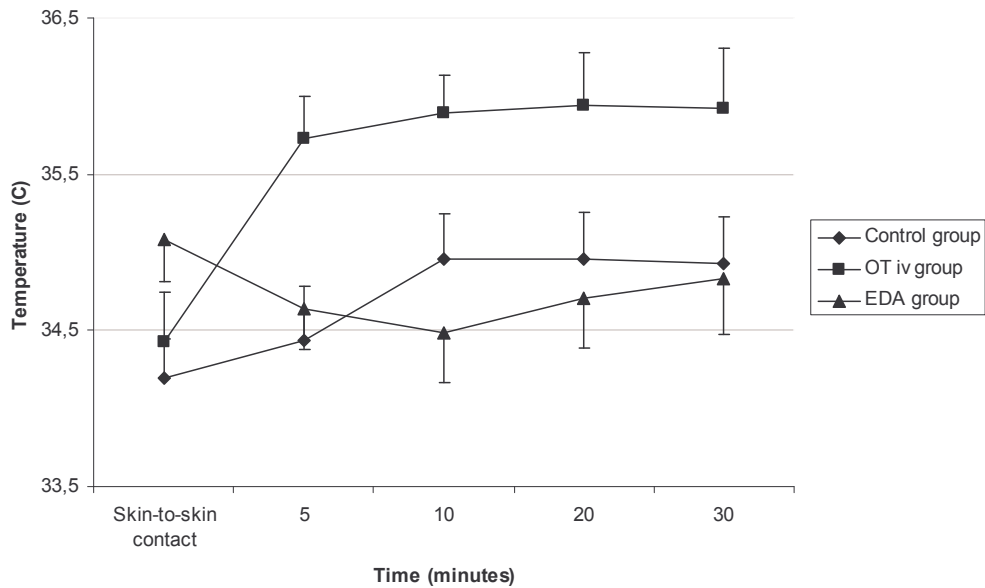
**Figure 6b.** The KSP scores (mean and standard deviation) of the fifteen subscales obtained two months postpartum. Shaded bars represent values of the mothers belonging to the EDA group (n=22). The y-axis starts with scores above 25.

#### **Newborn interscapular skin temperature (IV)**

The pattern of skin temperature in newborns two days postpartum was investigated in connection with a breastfeed. Furthermore, influences of EDA administration and oxytocin infusion during labour were studied. Temperature was measured immediately when the newborn was put skin-to-skin on the mother's chest and also measured at 5, 10, 20, and 30 minutes after skin-to-skin contact was established.

##### *Initial newborn interscapular skin temperature at skin-to-skin contact*

At the onset of skin-to-skin contact, the mean (standard error of the mean (SE)) interscapular temperature of the newborns belonging to the control group was 34.19 (SE=0.26) °C, to the oxytocin group 34.42 (SE=0.3) °C and to the EDA group 35.07 (SE=0.26) °C. The EDA group had a significantly higher temperature than the control group (p=0.025). In addition, in the EDA group, the age of the newborn was negatively correlated to the initial mean temperature, indicating that the younger the infant the higher the temperature (r = -0.46, p = 0.04) (Figure 7).



**Figure 7.** The mean (standard error of the mean) interscapular temperature (°C) of newborns to mothers of the control, the OT iv, and the EDA groups during a breastfeed two days postpartum. Temperature was recorded at start of skin-to-skin contact between mother and newborn and at 5, 10, and 30 minutes after start of skin-to-skin contact. Most of the newborns started to suckle the breast within the first five minutes after skin-to-skin contact.

*Temperature pattern during skin-to-skin contact and breastfeeding*

There was a significant increase in interscapular temperature (between temperature obtained at start of skin-to-skin contact and at 10 minutes after start of skin-to-skin contact) both in the control group (+0.91 (SE=0.2) °C, p=0.001) and in the oxytocin group (+1.47 (SE=0.37) °C, p=0.008). The temperature remained at a plateau level for the rest of the breastfeed. In the EDA group, by contrast, there was a significant decrease in interscapular temperature (between temperature obtained at start of skin-to-skin contact and at 10 minutes after start of skin-to-skin contact) (-0.62 (SE=0.22) °C, p=0.019). Thereafter the temperature remained relatively stable (Figure 7).

A mean value of the temperatures recorded at 10, 20, and 30 minutes for each group was calculated and then the various groups were compared. The mean temperature in the oxytocin group was significantly higher than that of the control group (p=0.048). Conversely, the temperature of the EDA group did not differ from the control group.

## 5 DISCUSSION

### Summary of findings

#### *Breastfeeding two days postpartum*

The major findings of the present study were that breastfeeding induced an immediate pulsatile release of oxytocin, and that prolactin levels rose significantly after 20 minutes of breastfeeding. The results also showed a positive correlation between oxytocin and prolactin levels, suggesting that the release of prolactin is influenced by oxytocin (I). Furthermore, maternal systolic and diastolic blood pressure fell during the breastfeed (II). According to the Karolinska Scales of Personality (KSP) the personality profile of the breastfeeding mothers was significantly influenced towards reduced anxiety and aggression, as well as increased socialisation when compared to a control group of non-pregnant and non-breastfeeding women (III). The interscapular skin temperature of the newborn rose significantly during breastfeeding (IV).

#### *Long-term follow up*

The long-term follow up study showed that blood pressure continued to fall in response to individual breastfeeding episodes over the six-month observation period. In addition, basal systolic and diastolic blood pressure fell by 15 and 10 mmHg, respectively (II). KSP ratings showed that the breastfeeding women remained significantly less anxious and more social than women in the normative sample during the 6-month follow up period (III).

#### *Influence of medical interventions during labour*

Median oxytocin levels were significantly lower in the women of the EDA<sup>OT</sup> group than in the women belonging to the OT iv, OT im and EDA<sup>non-OT</sup> groups. In addition, median oxytocin levels were decreased in a dose-dependent manner in all women having received oxytocin infusion in connection with labour (OT iv and EDA<sup>OT</sup> groups). Prolactin levels did not rise in response to suckling in women having received EDA without oxytocin infusion (EDA<sup>non-OT</sup> group). In contrast, the prolactin rise was larger and more sustained in mothers having received oxytocin infusion (OT iv and EDA<sup>OT</sup> groups) (I). Administration of EDA counteracted the personality changes towards less anxiety and more socialisation in the KSP at two days post partum observed in the control, OT iv and OT im groups. In contrast, oxytocin infusion dose-dependently reinforced the changes in

some of the personality items. After two and six months, the scores of the EDA group approached the KSP scores observed in the other groups (III).

Newborns to mothers who had received an EDA during labour did not show a rise in skin temperature in response to breastfeeding. On the other hand, the rise in skin temperature was larger in the group of infants whose mothers had received oxytocin infusion during labour (IV).

### **Methodological considerations**

The sample size of this study was small, but previous studies conducted by our group have shown that studies with small samples can yield important information if the selection criteria are strict (Nissen 1996, Ransjö-Arvidson et al. 2001, Widström et al. 1990). In this study, a homogenous group of women participated, which is a strength of the study (Polit and Hungler 1999). This study was not randomised, as in this particular setting it would have been unethical to randomise women during labour according to the different labour ward interventions.

It might be questioned whether the mothers were disturbed by the experimental interventions. We found, however, that mothers were able to concentrate on breastfeeding and their babies, and they did not pay attention to blood sampling or blood pressure measurements. Some mothers said they were happy to be able to help future mothers by participating in this study. Since mothers and fathers had the possibility to ask questions concerning birth, the baby and breastfeeding, many mothers and fathers said they felt special because of the extra attention they had received.

### **Physiological and behavioural responses to breastfeeding two days postpartum**

#### *Release of oxytocin*

In the present study, we could demonstrate that the suckling stimulus evoked an immediate and pulsatile release of oxytocin during a breastfeed two days after birth. The interval between the oxytocin pulses was 90 seconds. Interestingly, Hartmann and collaborators (Prime et al. 2007) have demonstrated that milk ejection occurred with 90-second intervals in response to breast-pumping. Oxytocin levels were not measured in their experiment, but the ejection of milk is likely to have been preceded by a rise of

oxytocin levels. Interestingly, in a previous study using a similar design to the one used in the present study, a pulsatile release of oxytocin was observed, and the amount of milk ingested by the infant (i.e. ejected by the mother) during the breastfeed was shown to be related to the number of oxytocin pulses recorded during the first 10 minutes of the experiment (Nissen et al. 1996). Taken together, these data suggest that milk is ejected in response to each single oxytocin pulse and that the amount of milk ejected was quantitatively related to the number of oxytocin pulses.

As described in the Background, it has been shown that strong stimulation of oxytocin producing cells, as occurs, e.g. during labour or suckling, leads to a synchronised firing of magnocellular oxytocin neurons, as well as to a consequent peak-shaped release of oxytocin into the circulation (Hatton and Tweedle 1982, Theodosis et al. 1986). Our results demonstrating that oxytocin is released in pulses at regular intervals support the assumption that the suckling stimulus coordinates the firing of the oxytocin producing cells, and consequently the release of oxytocin.

#### *Release of prolactin*

In this study, prolactin release occurred after 10 to 20 minutes of breastfeeding. A similar prolactin release profile has also been demonstrated in other studies (Lincoln and Paisley 1982, Nissen et al. 1996).

Prolactin is of importance for milk production, in particular during the initiation of lactation (Battin et al. 1985, Johnston and Amico 1986). In the present study, we could demonstrate a relationship between the duration of a single breastfeed and the amount of prolactin released. These data are in line with previous findings suggesting that the amount of suckling is of importance for milk production (Lawrence and Lawrence 2002, Zinaman et al. 1992). Further support for the important role of prolactin during lactation is given by the finding that the higher the prolactin levels are after three months of breastfeeding, the longer the mother will continue to breastfeed (Uvnäs-Moberg et al. 1990a).

Prolactin release is under an inhibitory control by PIF (dopamine) released from neurons in the tuberoinfundibular system (Lawrence and Lawrence 2002). Recently, it was suggested that oxytocin, which is released from oxytocinergic nerves in the pituitary,

plays an important stimulatory role in the regulation of prolactin secretion (McKee et al. 2007, Samson et al. 1986). The positive correlation between oxytocin levels and oxytocin variability, and prolactin levels on the other hand observed in the present study, supports the assumption that oxytocin plays an important role in the regulation of prolactin release during suckling.

Taken together, these results also show that oxytocin plays an important role during lactation, not only by inducing milk ejection via circulating oxytocin, but also by the stimulation of prolactin release via oxytocinergic nerves in the anterior pituitary.

#### *Release of oxytocin but not of prolactin in response to skin-to-skin contact*

Oxytocin is not only released during labour and suckling. It is also released by less intense sensory stimulation such as touch, massage, light pressure and warmth, as shown in animal experiments (Kurosawa et al. 1995, Lund et al. 1999, Lund et al. 2002, Stock and Uvnäs-Moberg 1988 Uvnäs-Moberg et al. 1993, Uvnäs-Moberg 1998a).

Similar results have been obtained in response to skin-to-skin contact and breast massage in mothers immediately after birth. When the infant massages the maternal breast, oxytocin is released in a “dose-dependent” manner, i.e. the more the newborn massages the breast, the more oxytocin is released (Matthiesen et al. 2001). The oxytocin release profile, however, induced by breast massage and skin-to-skin contact differs from that of breastfeeding, since it lacks the regular and frequent pulsatility typical of suckling-related oxytocin release. This may explain why prolactin is not released in response to skin-to-skin contact or breast massage, but in response to suckling (Yokoyama et al. 1994).

#### *Influence on maternal blood pressure*

Both systolic and diastolic blood pressure decreased significantly by almost 9 and 8 mmHg in response to the breastfeed performed two days postpartum. The results are in line with previously reported data showing a decrease in blood pressure in connection with breastfeeding two days postpartum (Nissen et al. 1998). A similar fall was observed in response to breastfeeding episodes during the six-month follow up period. Light et al. (2000) showed a similar decrease in blood pressure during breastfeeding when babies were between 6 and 24 weeks old.

In animal experiments, administration of intracerebroventricular oxytocin gives rise to a lowering of blood pressure (sometimes after a small initial rise) (Petersson et al. 1999b). Since oxytocin is released during breastfeeding, the decrease in blood pressure in response to breastfeeding is likely to be induced by oxytocin. Oxytocinergic nerve fibres originating in the PVN project to the NTS, which is an area of importance for regulation of autonomic nervous tone and cardiovascular control (Buijs 1983). We therefore assume that the decrease in blood pressure induced by breastfeeding is due to an inhibition of sympathetic nervous tone, as a consequence of oxytocin released, e.g. in the NTS.

In the present study, we observed a continuous fall of basal pre-breastfeeding blood pressure, and after six months of breastfeeding, the basal systolic and diastolic blood pressure was decreased by approximately 15 and 10 mmHg, respectively. The long-term decrease in basal pre-breastfeeding blood pressure may also be due to effects of oxytocin, since it has been shown that repeated administration of oxytocin to rats causes a decrease in both systolic and diastolic blood pressure: these effects last for weeks after the end of administration of oxytocin (Petersson et al. 1996b, Petersson et al. 1999b). The long-term decrease in blood pressure has been suggested to be caused by an oxytocin-mediated stimulation of the function of alpha-2-adrenoceptors. This type of receptor exerts an inhibitory effect on noradrenergic and adrenergic transmission in the CNS. Oxytocin has been demonstrated to diminish the firing of noradrenergic cells in the locus coeruleus (LC) via an increased function of the alpha-2-adrenoceptors (Petersson et al. 1998, Petersson et al. 2005a)

#### *Maternal psychological adaptations*

In the present study we were able to confirm that women undergo changes in their personality profile after birth. Data from several studies show that mothers become less anxious and less aggressive, as well as more inclined to social interaction after childbirth, according to the KSP personality inventory (Nissen et al. 1998, Uvnäs-Moberg et al. 1990b). Indeed, studies using the same inventory have demonstrated that these changes do not exist before birth, since these changes were observed neither at the beginning nor at the end of pregnancy (Sjögren et al. 2000, Sjögren et al. 2004). In the present study, we could demonstrate that the effect persisted during the entire observation period of six months. Since the KSP inventory measures personality traits, which are supposed to be



stable over life (Gustavsson et al. 1997b), the findings suggest that profound adaptations have occurred in women's behaviour and/or in their perceptions of themselves.

In previous studies, we demonstrated that changes in the KSP scores regarding socialisation and calm relate to circulating oxytocin levels. Assuming that circulating oxytocin levels reflect oxytocin release in the brain (Kendrick et al. 1986), the data suggest that endogenous oxytocin may play an important role in these adaptations (Nissen et al. 1998, Uvnäs-Moberg et al. 1990b). This assumption was also based on the fact that oxytocinergic nerves reach areas in the brain, such as the amygdala, in which levels of anxiety and social behaviour are controlled (Buijs 1983), as well as on the observation that administration of oxytocin to animals and humans stimulates social behaviours and induces anxiolytic-like effects (Domes et al. 2007a and b, Hollander et al. 2007, Keverne and Kendrick 1992 and 1994, Kirsch et al. 2005, Uvnäs-Moberg et al. 1994a).

The observed psychological adaptations seem to be related not only to oxytocin released into the brain during suckling, but also to the release occurring during labour since administration of EDA counteracted the effect. To induce such profound and long lasting effects on the personality profile as observed in the present study, large amounts of oxytocin must have been released. It is possible that oxytocin, released not only from oxytocinergic nerves within the brain, but also from dendrites and cell bodies of the magnocellular neurons, might have contributed to the effects. When oxytocin is released in this way, it might reach adjacent and distant areas in the brain by volume transmission (Ludwig and Leng 2006).

#### *Influence on newborns' skin temperature*

The newborn's skin temperature rose significantly in response to breastfeeding two days after birth. Several studies have demonstrated that skin-to-skin contact in the postpartal period leads to increased skin temperature in the infant (Christensson et al. 1992, Ransjö-Arvidson et al. 2001). For example, skin-to-skin contact 30 minutes after birth caused a rise in infants' skin temperature – in particular at peripheral sites (Bystrova et al. 2003). These results suggested that the increase of skin temperature is due to cutaneous vasodilatation as a consequence of decreased vasoconstriction (a phenomenon controlled by sympathetic nervous tone). In addition, the infant temperature was related to maternal

temperature, showing how intimately maternal and infant physiology are linked (Bystrova et al. 2007a).

### *Effects of oxytocin infusion and epidural analgesia*

In the breastfeeding study performed two days after birth, the release of circulating oxytocin was significantly and dose-dependently decreased in the women having received oxytocin infusions during labour. In addition, median oxytocin levels were lower in the women having received both oxytocin infusion and EDA than in the women having received oxytocin infusions alone. We have interpreted these data as follows: Infusion of exogenous oxytocin during labour, which gives rise to an unphysiologically high and non-pulsatile circulating oxytocin level, may influence the release of endogenous oxytocin, an effect that can still be observed two days after birth. Exogenous oxytocin infusion given in connection with labour may influence endogenous oxytocin release in two ways: Firstly, oxytocin infusion may exert an inhibitory feedback mechanism via oxytocin receptors which can be reached by circulating oxytocin and secondly a stimulatory effect of oxytocin via nervous transmission. The latter effect might be mediated by oxytocinergic stimulation of afferent nerves, e.g. those involved in the Ferguson reflex, and may therefore be blocked in response to EDA (Ferguson 1941). For a schematic illustration of the oxytocin mediated effects during labour and of the maternal adaptations two days after birth, please see Figures 9 and 10.

Prolactin levels were also influenced by the studied labour ward interventions; the breastfeeding-related prolactin pattern was inhibited by EDA and enhanced by oxytocin infusions. These results suggest that oxytocin released in the brain during labour is of importance for future milk production in the sense that oxytocin stimulates prolactin production via the nervous pathways in the anterior pituitary. When the positive influence on central oxytocin release mediated via the spinal cord is blocked as, e.g. in women having had an EDA (Goodfellow et al. 1983, Rahm et al. 2002), the prolactin producing cells may not be adequately stimulated during the “early sensitive period”. However, if extra exogenous oxytocin is given, this pathway may receive extra stimulation resulting in increased oxytocin release in the anterior pituitary and, consequently, increased prolactin secretion.

These data are in line with results obtained in women having had a caesarean section. These women not only showed less oxytocin pulses, but also a significantly reduced breastfeeding-related release of prolactin (Nissen et al. 1996). Both the women having had a caesarean section and those having had EDA have been reported to have breastfeeding problems (Beilin et al. 2005, Henderson et al. 2003, Rowe-Murray and Fisher 2002, Torvaldsen et al. 2006, Wiklund et al. 2007). A common mechanism of breastfeeding-related problems may be the reduced prolactin secretion, since prolactin has an important role in the initiation of milk production.

The behavioural adaptations, observed in the present study were also influenced by the medical interventions. The reduction of anxiety and aggression and the increased levels of socialisation in the breastfeeding mothers was not observed in the women having had an EDA. Oxytocin infusions in connection with birth had a positive effect on some of the subscales, when administered by itself and when combined with EDA. In the latter case, the absent behavioural changes were partially restored, particularly after two and six months. These data further support the important role of oxytocin in connection with labour for the development of the maternal behavioural adaptations. If the women receive an EDA, the release of oxytocin in the brain normally occurring during labour might be inhibited, and as a consequence, the maternal adaptations would be underdeveloped. However, if exogenous oxytocin is administered, circulating oxytocin levels rise and the afferent nerves involved in the Ferguson reflex receive extra stimulation whereby the inhibition by the EDA may be partly overcome (For a schematic illustration, see Figures 9 and 10).

These results are in fact similar to the results obtained from animal studies, which suggest that oxytocin released during labour is of crucial importance for the development of maternal behaviour and bonding to the young (Kendrick et al. 1987, Keverne and Kendrick 1992 and 1994, Pedersen and Prange 1979, Pedersen et al. 1982). In both heifers and sheep, administration of EDA has been demonstrated to delay the development of maternal behaviour and also bonding to the young (Krehbiel et al. 1987, Levy et al. 1992, Williams et al. 2001). During normal labour, the release of oxytocin is reinforced when the head of the fetus is pressing against the cervix. The pressure activates sensory nerves, which, via the spinal cord, transmit impulses to the SON and PVN to induce a release of oxytocin (Ferguson 1941). Certain types of analgesic methods, such as

spinal, peridural and epidural anaesthesia, act by inhibition of nervous transmission in the spinal cord. As a consequence, oxytocin release is inhibited not only into the circulation but also into the brain and, thereby, in the development of maternal behaviour and bonding (Levy et al. 1992, Williams et al. 2001). Administration of oxytocin into the brain restores the inhibited maternal behaviour and bonding to the young (Levy et al. 1992).

The data are also supported by previous findings showing that circulating oxytocin levels are decreased during labour in women having received EDA, which often leads to the need for intravenous oxytocin to augment labour (Goodfellow et al. 1983, Rahm et al. 2002).

Infants whose mothers had received EDA also failed to raise their skin temperature in response to breastfeeding two days after birth. In contrast, the effect was enhanced in infants of mothers having received oxytocin infusions. The reason for this is not known. However, two possible explanations exist. It is possible that both the oxytocin and the constituents of the EDA (marcain and sufentanil) could have passed the placental barrier during labour and influenced the newborns' regulatory centres (Krishna et al. 1997, Loftus et al. 1995, Malek et al. 1996). A second possible explanation would be that the effects are mediated by a change in maternal physiological and/or psychological interaction.

### **General aspects of physiological and behavioural adaptations during labour, in the postpartum period and during breastfeeding**

Since oxytocin is released in parallel into the circulation and into the CNS oxytocin is likely to induce central effects during labour, breastfeeding and also in the postpartum period (Kendrick et al. 1986). The effect patterns caused by oxytocin in connection with labour and breastfeeding differ slightly, due to the needs in the different situations. Blood pressure is increased during labour, whereas breastfeeding is related to a decrease in blood pressure ( Light et al. 2000, Nissen et al. 1996). Oxytocin also contributes to the increased pain threshold during labour (Komisaruk and Sansone 2003).

The short- and long-term decrease in blood pressure and the changes in the maternal personality profile that were described in papers II and III are expressions of a psycho-

physiological pattern that help women adapt to motherhood. Women are “helped” in their future role as caregivers by mental adaptations, making them calmer and more inclined to social interaction, as well as by physiological adaptations facilitating milk production. These adaptations are likely to be caused by oxytocin released into the brain during labour, in the postpartum period and also during breastfeeding (Kendrick et al. 1986, Keverne and Kendrick 1994) and may represent expressions of the maternal behaviour induced by oxytocin release during labour and in the postpartum period as seen in other mammals. The decrease in blood pressure observed in response to breastfeeding is but one expression of a more generalized anti-stress pattern, which also includes decreased levels of anxiety and cortisol levels, both in response to an individual breastfeeding session and also in a more long-term perspective (Altemus et al. 1995, Altemus et al. 2001, Amico et al. 1994, Heinrichs et al. 2001, Heinrichs et al. 2002, Nissen et al. 1996).

The breastfeeding-related anti-stress pattern is an adaptive response *per se*, but is also part of a more fundamental physiological change taking place in the mother, by which nutrient assimilation and anabolic metabolism is reinforced. It is of importance for the breastfeeding mother to use energy in an optimal way in order to be able to produce milk for the infant and to also support her own needs (Uvnäs-Moberg 1989). As demonstrated previously, breastfeeding is related to an activation of the vagal nerve and enhanced gastrointestinal function, which leads to an optimized digestion and anabolic metabolism (Uvnäs-Moberg et al. 1994b Uvnäs-Moberg 1996, Widström et al. 1988).

The beneficial effects induced by breastfeeding may explain why breastfeeding mothers differ from bottle-feeders, who have been shown to be less interactive and responsive to their infants, as well as to have an increased stress reactivity in the skin conductance test and higher blood pressure (Dunn and Richards 1977, Mezzacappa et al. 2005).

An important question is whether the long-term behavioural and physiological effects induced during labour, in the postnatal period and during breastfeeding – which are caused by a repetitive release of oxytocin – ever completely disappear. The saying “Once a mother, always a mother” might have a neuroendocrine or physiological underpinning.

Subtle changes in signalling functions induced during pregnancy and breastfeeding and in the postpartum period might become uncovered and reappear during a subsequent

pregnancy or breastfeeding period. It has been shown, for example, that women have lower blood pressure during the second pregnancy than during the first (Strevens et al. 2001). This difference occurs despite an age-related increase in blood pressure, and suggests that an increased sensitivity of alpha-2-adrenoceptors might become apparent in situations of renewed stimulation, by estrogens during pregnancy and oxytocin during lactation (Petersson et al. 1998, Petersson et al. 2005). Such long-term alpha-2-adrenoceptor mediated anti-stress effects may explain, e.g. why women having given birth to children and having breastfed are “dose-dependently” protected from hypertension (Lee et al. 2005) and myocardial infarction (Stuebe et al. 2009) later on in life. If so, exposure to oxytocin may not only be of adaptive value during pregnancy and lactation, but may be of importance for women’s health in a much longer time perspective.

#### *Effects of skin-to-skin contact*

Data from other published and unpublished findings based on the present study show that skin-to-skin contact before suckling contributes to the maternal anti-stress effects induced by breastfeeding; both blood pressure and cortisol levels decrease in response to breastfeeding (Johansson et al. 2009, data to be published). The infant is also influenced by the sensory stimulation caused by interaction with the mother. An increased peripheral circulation was demonstrated in newborn infants being in skin-to-skin contact with their mothers (Bystrova et al. 2003). A similar effect was demonstrated in the present study in response to breastfeeding two days after birth.

We suggest that the sensory stimulation induced by skin-to-skin contact and/or suckling inhibits sympathetic nervous tone in both mother and newborn by way of activation of the oxytocinergic pathways projecting from the PVN to the NTS (Buijs et al. 1985). By inhibition of the activity in various aspects of the sympathetic nervous system involved in the control of cardiovascular tone (e.g. the NTS), cutaneous circulation increases in the baby and blood pressure decreases in the mother, which represent two different consequences of decreased vascular tone.

The decrease in maternal blood pressure observed in response to skin-to-skin contact and to breastfeeding is, as mentioned above, just one expression of a generalized effect pattern also involving increased social interaction, reduced levels of anxiety and lowered levels of

cortisol (Amico et al. 1994, Heinrichs et al. 2001, Nissen et al. 1996, Nissen et al. 1998). The rise in skin temperature in the infant is probably associated with a more generalized effect pattern also involving increased social interaction, well-being, calm and relaxation, although these variables were not measured in the present study (Christensson et al. 1992 Christensson et al. 1995, Erlandsson et al. 2007, Gray et al. 2000).

The concept of an “early sensitive period”, during which extra sensory interaction between mother and young results in a long-term promotion of positive social interaction between mother and young, was coined by Klaus and Kennel (Kennel et al. 1975, Klaus et al. 1972). In a recent study, two hours of skin-to-skin contact after birth was followed by better interaction between mother and infant at the age of one year and also by reduced stress behaviour in the infant (Bystrova et al. 2009). These results indicate that the sensory stimuli exchanged between mother and infant in the early postpartal period, when oxytocin levels are still high, induce long-term effects. Similar long-term effects have also been demonstrated in animals in response to postnatal extensive sensory interaction between mother and young (Liu et al. 1997). These changes have been attributed to epigenetic phenomena that are certain stimuli, e.g. sensory stimulation in the newborn period may activate or deactivate certain genes. Such effects may even be transferred between generations, since rat pups having received extra amounts of sensory stimulation in the newborn period interact more with their own pups when they themselves become mothers (Francis et al. 1999, Francis et al. 2002). It is possible that the long-term effects caused by skin-to-skin contact in mother and infant during the postpartal period also involve such epigenetic mechanisms.

Recently, it was demonstrated, that ward routines such as CS was associated with epigenetic phenomena (Schlinzig et al. 2009).

#### *Consequences of oxytocin infusion and epidural analgesia in connection with labour*

The present data indicate that administration of oxytocin and EDA during labour has effects beyond the effects that were originally intended, i.e. stimulation of contractions and pain relief during labour.

Epidural analgesia in connection with labour counteracted the development of maternal psychological adaptations as well as the suckling related prolactin secretion two days post



partum. Infusion of exogenous oxytocin had the opposite effect, since it reinforced the psychological adaptations and suckling related prolactin release and to a certain extent reversed the effects caused by EDA. On the other hand, oxytocin infusions dose-dependently decreased basal oxytocin levels. In addition, the reactivity of the HPA-axis and also of blood pressure seems to be increased in the mothers having received oxytocin infusions (Johansson et al. 2009, data to be published). Taken together these data indicate that infusion of exogenous oxytocin has a twofold effect; it inhibits basal circulating oxytocin levels and the activity in the oxytocinergic neurons that inhibit stress reactivity (leading to an increased activity of the HPA-axis and higher blood pressure) but reinforces maternal mental adaptations and prolactin release. The first effect of exogenously infused oxytocin may be mediated via receptors in the circulatory system. The second effect may be indirectly mediated by neurogenic mechanisms (For schematic illustrations, please see Figures 9 and 10).

The effects of EDA and oxytocin infusion were recorded two days post partum i.e. two days after the interventions were administered. We do not know if similar effects can be recorded even later, but ward routines such as skin-to-skin contact or separation in the post partal period give rise to effects, which can be observed after one year (Bystrova et al. 2009). It is not unlikely that medical interventions during labour might also cause long lasting effects since they are applied during the “early sensitive period”.

It might be tempting to substitute the loss of endogenous oxytocin following administration of EDA by administration of exogenous oxytocin. The finding of two partly opposing effects of exogenous oxytocin makes this solution more complicated. Nature has shaped the oxytocin release as to timing and amount and the pattern of oxytocin-related effects in connection with birth since the origin of humankind. Similar systems operate in all mammals (Keverne and Kendrick 1994). To administer too much oxytocin or, even worse, more long-lasting oxytocin variants may be maladaptive since the levels of anxiety and aggression in the mother may become too low and the level of social interaction and bonding abnormally strong. This would also interfere with the development of the infant’s social skills and ability to handle stress either directly via transfer of oxytocin to the infant via the circulation (Malek et al. 1996) or mother’s milk (Takeda et al. 1986) or indirectly via an altered pattern of maternal-infant interaction. Our finding of an influence of the newborn’s skin temperature in connection with



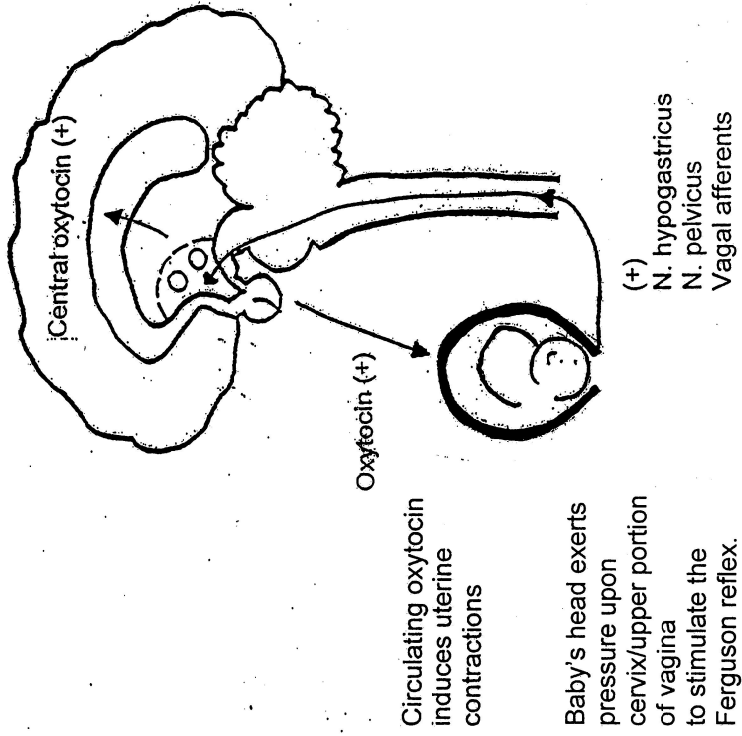
breastfeeding two days after birth after administration of oxytocin infusion and EDA may indicate that such effects exist.

## **6 CONCLUSION**

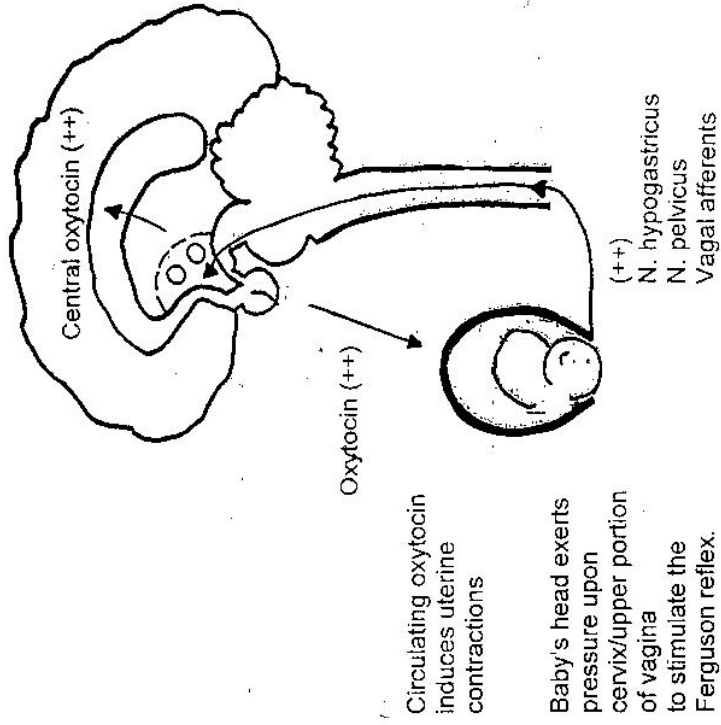
This study confirms the existence of postpartum physiological and psychological adaptations in mothers and newborns in the short- and long-term perspective. It also shows that administration of exogenous oxytocin and EDA during labour influenced these effects beyond those that were originally intended (i.e. augmentation of labour and pain relief). Studies are needed to confirm the results obtained in the present study. If the data are confirmed, further studies are needed to explore such effects of medical interventions in mothers and their newborns.

## 7 SCHEMATIC ILLUSTRATIONS

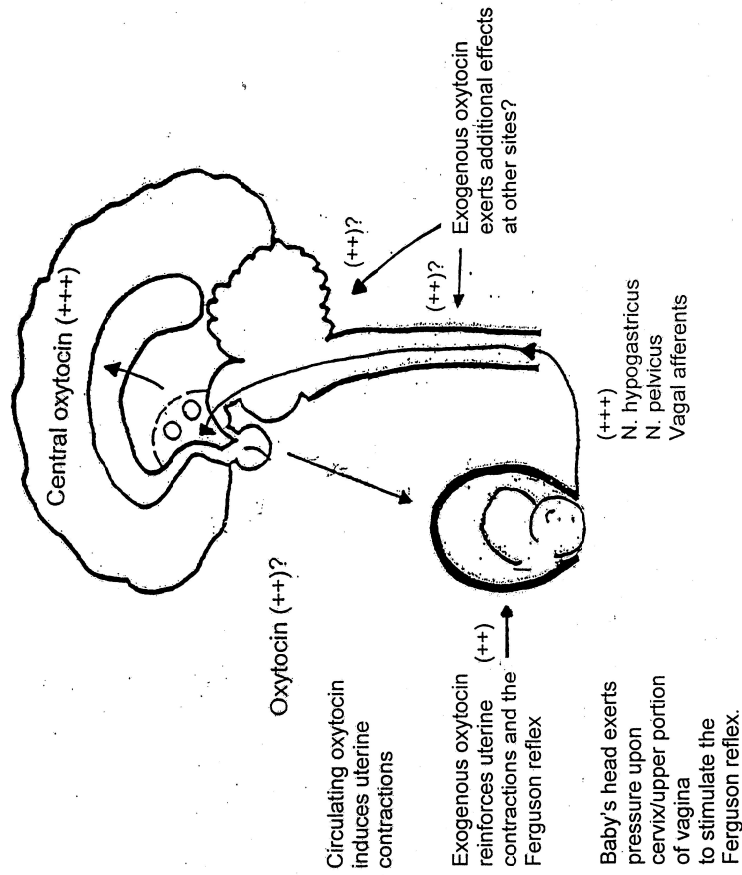
a) Oxytocin-mediated effects during the 1<sup>st</sup> stage of labour.



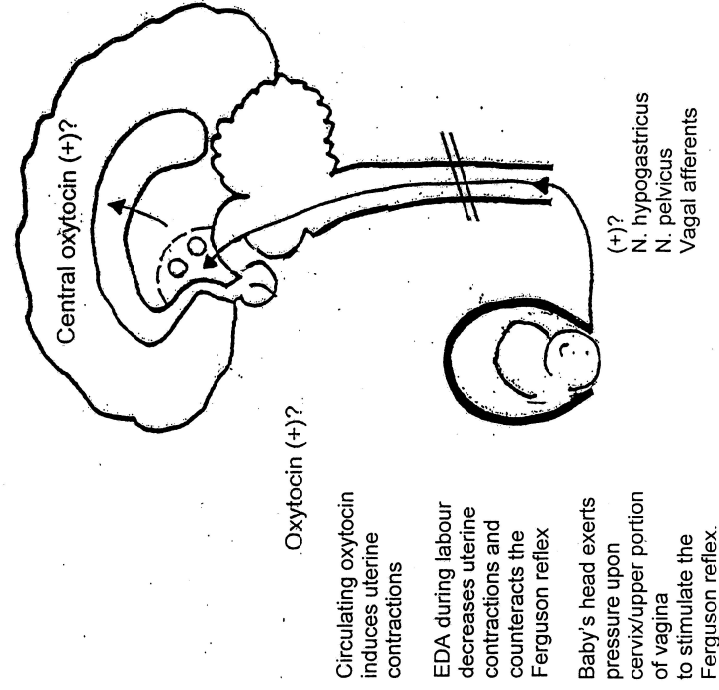
b) Oxytocin-mediated effects during the 2<sup>nd</sup> stage of labour.



c) Oxytocin-mediated effects during labour in women receiving exogenous oxytocin infusion.



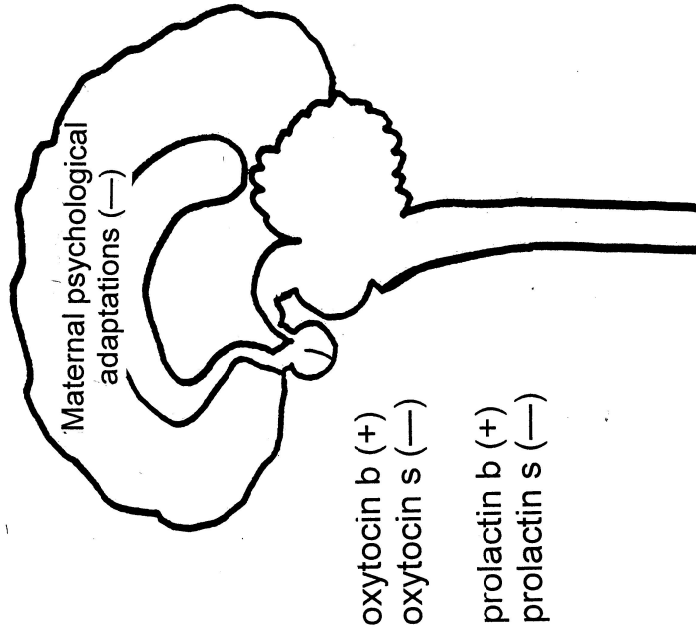
d) Oxytocin-mediated effects during labour in women receiving epidural analgesia (EDA).



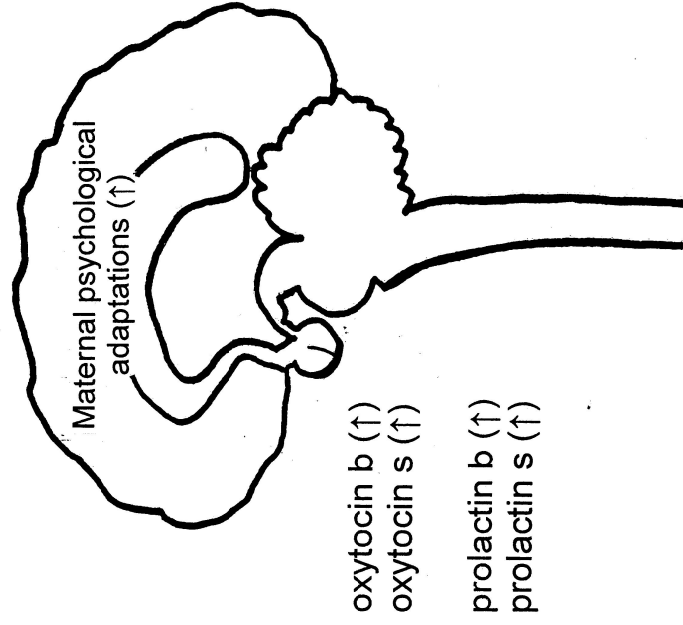
**Figure 9 a-d.** The schematic illustrations demonstrate oxytocin-mediated effects in women a) during the 1<sup>st</sup> stage of labour, b) during the 2<sup>nd</sup> stage of labour, and in women c) who receive exogenous oxytocin infusion during labour and d) who receive epidural analgesia (EDA) during labour. Effects of circulating oxytocin on uterine contractions and on effects in the brain are depicted.

Explanation of symbols: (+)?, (+), (++) , (+++) increasing levels of oxytocin.

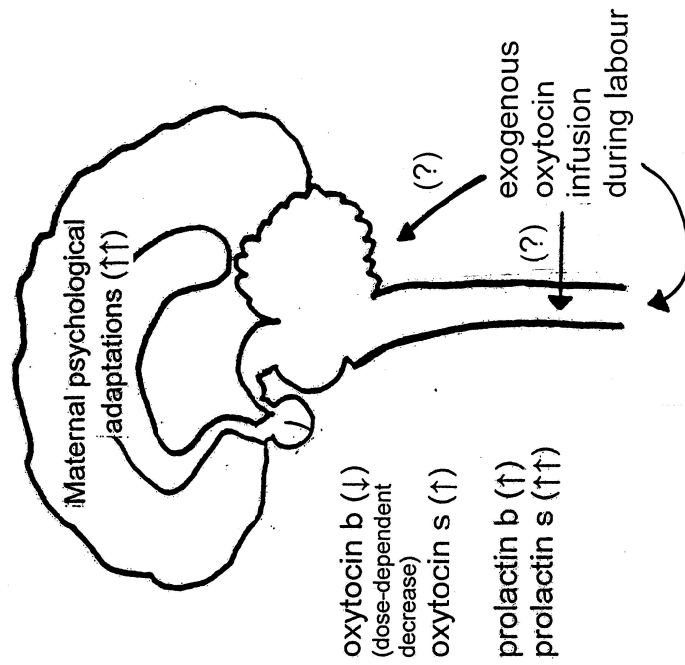
a) "Brain" of non-lactating women.



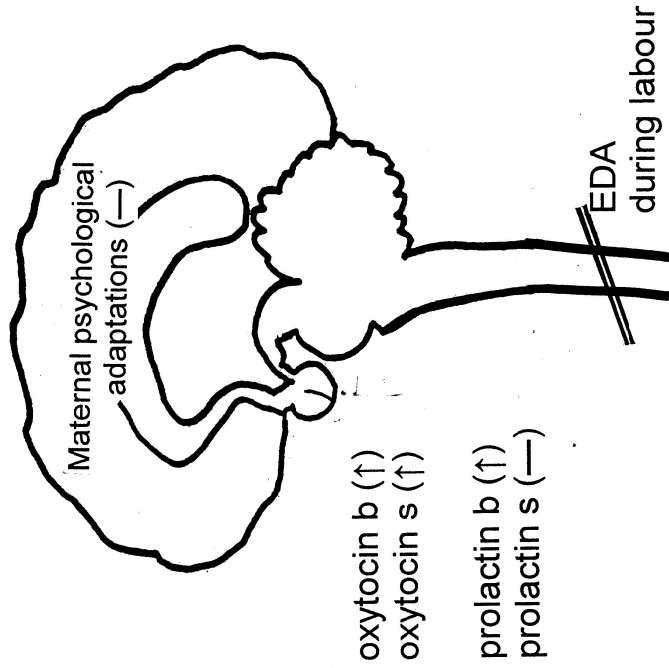
b) "Brain" of lactating women two days postpartum.



c) "Brain" of lactating women two days postpartum who received oxytocin infusion during labour.



d) "Brain" of lactating women two days postpartum who had received epidural analgesia (EDA) during labour.



**Figure 10 a-d.** The schematic illustrations demonstrate the "brain" a) of non-lactating women, b) of lactating women two days postpartum, c) of lactating women two days postpartum who had received exogenous oxytocin infusion during labour and d) of lactating women two days postpartum who had received EDA during labour. Effects on maternal psychological adaptations as well as on basal and suckling related oxytocin and prolactin levels are demonstrated.

Explanation of symbols: (—) non-existing, (+) existing, ↑ increase, ↑↑ reinforced increase, ↓ decrease.

Explanation of abbreviations: oxytocin b – basal oxytocin plasma levels, oxytocin s – suckling-related oxytocin plasma levels; prolactin b – basal Prolactin plasma levels, prolactin s – suckling-related prolactin plasma levels.

## 8 ACKNOWLEDGEMENTS

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