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Hormones and fluid balance during pregnancy, labor and post partum

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Abstract

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The aim of this thesis was to determine any association between plasma oxytocin and vasopressin concentrations and renal water and sodium excretion during normal pregnancy. In addition to investigate changes in concentrations of estradiol, progesterone, oxytocin, cortisol, and glucose in the blood before and in the nearest hours after delivery and if treatment with oxytocin affected these concentrations and the fluid balance during the different stages of labour.

Oxytocin, vasopressin, estradiol, progesterone, and cortisol were analysed in blood plasma or serum by radioimmunoassay or ELISA: serum glucose, and osmolality, and sodium in plasma and urine were analysed by standard laboratory techniques.

Fifty-seven women were studied during pregnancy and fifty-one during parturition and post partum. The low plasma vasopressin and increasing plasma oxytocin concentrations with unchanged water and sodium excretion indicate that oxytocin assists vasopressin in concentrating urine during pregnancy.

Plasma vasopressin concentration continued to be low during parturition and post partum. Urine flow and concentration was unrelated to changes in plasma sodium concentration, indicating regulation of fluid balance during parturition was different to the non-gravid state. Women with weak myometrial contractions during parturition (slow progress of labour) reacted differently than women with normal parturition and a group of women with fast progress of labour. The group with slow labour had lower serum estradiol concentration in the latency phase and became hyponatremic. Pulsatile and continuous oxytocin infusions were both effective in the treatment of slow progress of labour. A lower amount of oxytocin was needed to affect delivery when given as pulsatile infusion.

Serum cortisol and glucose concentrations were high during labour and cortisol level remained elevated after delivery and glucose concentration reached the highest levels (12 mmol/L) at the same time. Insulin resistance together with the long time of elevated cortisol concentration partly explained the high glucose concentration. In conclusion, fluid balance is not regulated according to the usual sensitive osmotic and volumetric influence on vasopressin release from the neurohypophysis during pregnancy and parturition. Parturition involves a change from one demanding condition, pregnancy, to another, lactation. Parturition and the hours directly after delivery are a turbulent period involving considerable stress.

Keywords: cortisol, estradiol, glucose, labour, osmolality, oxytocin, parturition, pregnancy, pregnancy-induced hypertension, progesterone, vasopressin

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In memory of my beloved father Ove

*I lift up my eyes to the hills -- where does my help come from?
My help comes from the Lord, the Maker of heaven and earth.
He will not let your foot slip -- He who watches over you will
not slumber; indeed, He who watches over Israel will neither
slumber nor sleep.*

*The Lord watches over you -- the Lord is your shade at your
right hand; the sun will not harm you by day, nor the moon by night.*

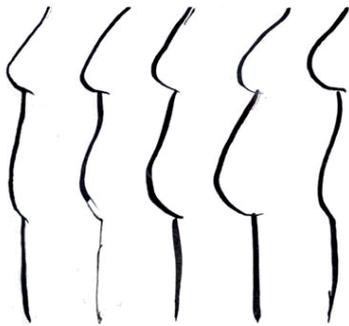
The Lord will keep you from all harm

*He will watch over your life; the Lord will watch over your
coming and going both now and forever more.*

Psalm 121

*To Anders, Rebecka, Cecilia,
Desirée, Mathias, Jonatan &
Elly with love*

Is normal normal?



Cecilia R. Nyström

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I** Risberg A, Larsson A, Olsson K, Lyrenäs S and Sjöquist M. (2004) Relationship between urinary albumin and albumin/creatinine ratio during normal pregnancy and preeclampsia. *Scand J Clin Lab Invest*, 64:17-24
- II** Risberg A, Olsson K, Lyrenäs S, and Sjöquist M. (2009) Plasma vasopressin, oxytocin, estradiol, and progesterone related to water and sodium excretion in normal pregnancy and gestational hypertension. *Acta Obstet et Gynecol*, 88:639-646
- III** Risberg A, Sjöquist M, Kaj Wedenberg, Larsson A and Olsson K. (2009) Hormonal changes before, during, and after delivery related to treatment with oxytocin and opioids. *In manuscript*
- IV** Risberg A, Sjöquist M, Larsson A, Wedenberg K and Olsson K. (2009) Fluid balance during parturition and the immediate puerperium. *In manuscript*

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Abbreviations

ACTH	Adrenocortical hormone
ADH	Antidiuretic hormone
BMI	Body mass index, kg/m ²
EIA	Enzyme immunoassay
MAP	Mean arterial pressure
NT	Normotensive
i.e.	That is
ns	Non significant
PIH	Pregnancy induced hypertension
PP	Post partum
RAS	Renin Angiotensin System
RIA	Radioimmunoassay
SEM	Standard Error of Mean
SPSS	Statistical Package for Social Sciences
WHO	World Health Organisation

Introduction

The female body undergoes major but transient changes during pregnancy, parturition, aftercare, and postpartum that affect the genital organs and the hormonal system, the cardiovascular system, and salt and water balance. Disturbances in the cardiovascular system and the regulation of fluid balance can lead to changes in blood pressure and to hypo- or hypertension. Imbalance in salt and fluid regulation is common and can cause oedema. During parturition, demands on the regulatory systems further increase. Labour implies physical work, which may be prolonged, pain, which may be severe, and anxiety. Therefore, different methods of accelerating delivery have been developed and are commonly practiced, as are the use of pharmacological and non-pharmacological methods of pain relief. The methods are not universally beneficial but may cause adverse effects on the maternal body and foetus and disturbances in the regulation of e.g. uterine contractions, blood pressure, fluid balance, and placental function. After delivery of the baby, the placenta is detached within minutes and the secretion of placental hormones into the female circulation stops. This triggers the production of milk from the breasts and the maternal organism adjusts to the state of lactation or to non-pregnancy.

In this thesis, the roles of vasopressin and oxytocin during pregnancy and parturition were studied with regard to fluid balance. The effects of oxytocin, and of estradiol, progesterone, cortisol, and glucose during and after parturition were investigated to determine if treatment with oxytocin infusions and analgesics affected the progress of labour and the first 27 hours postpartum.

Pregnancy

Blood pressure

The rapidly growing foeto-placental unit has a high metabolic activity that demands a rich blood supply. Several other organs increase in size and metabolic activity demanding extra blood and the peripheral vascular bed dilates. The retention of salts and water and the increased production of plasma proteins expand the extracellular and plasma volumes. Shortly before term, the maternal plasma volume is about 30% above normal and the red

blood cell mass increases by about 15%. Therefore, at parturition, the mother has about 1-2 litres more blood than in the non-pregnant state. About one fourth of this is normally lost through bleeding, thereby providing a safety factor for the mother (1). Some remaining extra blood volume is needed for the blood supply to the breasts at the onset of lactation.

Arterial blood pressure decreases during pregnancy despite expanded blood volume and increased activity of the Renin - Angiotensin-Aldosterone – System (RAAS), as the vascular sensitivity to angiotensin II is reduced. The cause of this refractoriness is unclear. The RAAS will not be discussed further in this thesis.

Fluid balance

During normal human pregnancy, the maternal body accumulates water, electrolytes, and nutrients in order to meet the needs of the mother and the fetus. Total body water increases by 6-8 litres and plasma osmolality decreases about 10 mosm/kg below non-pregnant levels. The thresholds for thirst and vasopressin release decrease during the first trimester (2, 3). In the first two trimesters, regulation appears normal around the new set-point, but during the last trimester, regulation becomes more vulnerable, e.g. a water load is not easily excreted (4) and the release of vasopressin in response to hypertonic NaCl solutions is attenuated (5).

Renal perfusion and filtration increase markedly during pregnancy, perhaps due to the necessity of excreting extra waste products. The increased metabolism and respiratory rate leads to increased evaporation of water and fluid intake usually increases.

In addition, several special alterations of renal function occur. First, the renal tubules re-absorptive capacity of sodium, chloride, and water increases as much as 50% due to increased production of steroid hormones by the placenta and adrenal cortex. Second, glomerular filtration rate can increase up to 50% during pregnancy, which tends to increase the rate of water and electrolyte excretion in urine. When all these effects are considered, the normal pregnant woman ordinarily accumulates only about 3 kg of extra water and salt. With the exchange of salt and water, both input and excretion, the net effect is that salt, water, proteins, and fat are accumulated.

Vasopressin and oxytocin

Vasopressin and oxytocin are synthesised in nerve cells in the hypothalamus and transported by nerve axons to the neurohypophysis, where they are stored and then secreted into the blood. Both vasopressin and oxytocin are oligopeptides with nine amino acids, seven of which are identical. Vaso-

pressin has three known receptors, V1a, V1b, and V2, and oxytocin only one (6). The peptides can act on each other's receptors, although their affinity and efficiency differ so the proper ligand is more effective (7, 8). The V1 and oxytocin receptors are distinctly different from V2. The V1 and oxytocin receptors are G-protein-coupled with seven trans-membrane domains. V1a is found in many tissues, including the uterus, mammary glands, and blood vessels. V1b is found in the ACTH-producing cells of the anterior pituitary. The V2 receptor is found in the distal tubules and the collecting ducts of the kidneys and is responsible for the antidiuretic effect of vasopressin. Aquaporin 2 channels must be present in the cell membranes in order for vasopressin to exert its antidiuretic effect.

Vasopressin is a potent vasoconstrictor and acts on the vascular smooth muscle. Normally, shortly after vasopressin is secreted, the vasoconstriction is a reality. However, vasopressin concentration may rise to high levels during severe haemorrhage (9). The ensuing vasoconstriction helps to prevent further blood-loss and to stabilise blood pressure. The V1a receptor is expressed in the uterine smooth muscle, but it is not up regulated near term, in contrast to the oxytocin receptor.

Oxytocin is best known for causing myometrial contractions at parturition and milk let down. Oxytocin secretion has a diurnal rhythm with increases secretion during the night in non-pregnant subjects (10). Immediately before parturition in humans, estrogen levels rise and oxytocin receptor synthesis increases. When estrogen, and not progesterone, dominates the uterus, the oxytocin receptors starts to increase in number and sensitivity. Apart from its effects on smooth muscle cells, oxytocin has a weak antidiuretic effect, probably due to action on the aquaporin 2 water channel in the kidneys (11-13).

Placenta and its hormones

The placenta is a highly vascularised organ formed from both maternal and embryonic tissues, and provides oxygen and nutrients for the foetus, and transfer of waste products from foetal to maternal blood circulation. In addition, the placenta is an endocrine organ.

The production of steroids from the ovaries is superseded by production from the placenta early in pregnancy. The endocrine function of foetal placental tissue maintains (14) a calm gravid uterus,(15) alters maternal physiology to ensure foetal nutrition, alters maternal pituitary function, and stimulates mammary gland development to ensure milk production. In combination with the foetal adrenals, the placenta production of hormones is considered to determine the time of delivery.

Human chorionic gonadotropin (hCG) is the first hormone produced by the placenta and has a similar function as the luteinising hormone secreted by the pituitary gland. Its most important function is to prevent involution of the corpus luteum at the end of the menstrual cycle. Instead, it causes the corpus luteum to secrete even larger quantities of progesterone and estrogens during early pregnancy. As a result, menstruation is prevented and the endometrium continues to grow and store large amounts of nutrients rather than being shed during menstruation.

The secretion of estrogens and progesterone is maintained to ensure the function of the cells, which is necessary for the early development of the foetus. If the corpus luteum is removed before approximately the 7th week of pregnancy, spontaneous abortion usually occurs, sometimes even up to the 12th week (1).

Estrogens

Estrogens and progesterone, as with most other placental hormones, are secreted by the syncytial trophoblast cells of the placenta (16). Toward the end of pregnancy, the daily production of placental estrogens has increased about 30 times. However, placental secretion of estrogens is different from secretion by the ovaries. The estrogens are not synthesized *de novo* from basic substrates in the placenta. Instead, they are formed almost entirely from androgenic steroid compounds, dehydroepiandrosterone and 6-hydroxydehydroepiandrosterone from the adrenal glands, derived from both mother and foetus. These androgens are transported by the blood to the placenta and converted by the trophoblast cells into estradiol and estriol.

The cortices of the foetal adrenal glands are relatively large, and the primary function appears to be secretion of dehydroepiandrosterone during pregnancy.

Progesterone

Progesterone is essential for a successful pregnancy. In addition to being secreted in moderate quantities by the corpus luteum at the beginning of pregnancy, it is secreted in larger quantities by the placenta, averaging about a 10-fold increase during the course of pregnancy. The regulation of progesterone is not fully understood, but is related to the supply of cholesterol in placenta: placental steroidogenesis differs from that in the adrenal cortex, ovaries, and testis in that cholesterol is transported into the placental mitochondria by a mechanism independent of StAR protein (16). Thus, the first step in steroidogenesis is not regulated by a rate-limiting step in the placenta as it is in other steroidogenic glands.

Placental progesterone production does not require foetal contribution. Consequently, progesterone levels cannot be used as a measure of foetal health.

The special effects of progesterone essential for normal progression of pregnancy include:

- Progesterone specifically increases the secretions of the mother's fallopian tubes and uterus to provide appropriate nutritive matter for the developing blastocyst: there is also reason to believe that progesterone affects cell cleavage in the early developing embryo.
- Progesterone cause decidual cells to develop in the uterine endometrium, and these cells play an important role in the nutrition of the young embryo.
- Progesterone decreases the contractility of the pregnant uterus.
- Progesterone secreted during pregnancy helps estrogens to prepare the breasts for lactation (9).

Other hormones in pregnancy

Almost all endocrine glands in the mother react to pregnancy. Among those hormones are parathyroid hormone and relaxin. The anterior pituitary gland enlarges at least 50% during pregnancy and increases production of the growth hormone, ACTH, thyrotropin, and prolactin. The hormones from the anterior pituitary increase stimulation of their target organs, except the follicle-stimulating and luteinising hormones, which are suppressed as a result of the inhibitory effects of estrogen and progesterone from the placenta.

The hypothalamic-hypophysis-adrenal axis

The rate of adrenocortical secretion of the glucocorticoids increases throughout pregnancy and pregnant women usually have about a two-fold increase in the secretion of aldosterone, reaching a peak at the end of gestation. This, along with the actions of estrogens, causes the renal tubules to retain sodium, thereby, accumulating sodium and water.

In human pregnancy, the maternal plasma concentration of cortisol gradually increases from the 8th to 36th week of gestation and shows a marked rise until onset of labour (17). The diurnal variation of plasma cortisol levels is maintained in pregnancy: a morning cortisol level in non-pregnant state is > 450 nmol/L, during daytime and < 50 nmol after midnight (16). The highest plasma concentrations of cortisol are at the beginning of labour (18).

Pregnancy-induced hypertension

Pregnancy-induced hypertension, and especially the most serious form called eclampsia, has been a dreaded complication of pregnancy since Hippocrates' time (19). In the 1840s, eclampsia was discovered to be accompanied by

proteinuria, and in the late nineteenth century, the technique of indirect measurement of arterial blood pressure was developed. Hypertension and proteinuria became accepted as warning signs of eclampsia (preeclampsia), and screening of pregnant women was introduced (20). The commonly used term, pregnancy-induced hypertension, encompasses hypertension both with proteinuria (preeclampsia) and without proteinuria (gestational hypertension).

About 5% of all pregnant women undergo a rapid rise in arterial blood pressure to hypertensive levels during the last few months of pregnancy. Preeclampsia is often characterised by excess salt- and water retention by the mother's kidneys, bodyweight gain, and development of oedema. The cause may be impaired function of the vascular endothelium, and arterial spasm occurs in many parts of the body, especially in the kidneys, brain, and liver. Both the renal blood flow and the glomerular filtration rate decrease. The renal effects also include thickened glomerular tufts that contain a protein deposit in the basement membranes.

Although many attempts have tried to prove preeclampsia is caused by excessive secretion of placental or adrenal hormones, there is still lack of evidence. Another theory is that preeclampsia results from autoimmunity or allergy caused by the presence of the foetus. In support of this, the acute symptoms usually disappear within a few days after the birth of the baby. There is also evidence that preeclampsia is initiated by insufficient blood supply to the placenta (16), resulting in release of substances that can cause dysfunction of the maternal vascular endothelium.

Although the factors that link reduced placental blood supply with maternal endothelial dysfunction are still uncertain, some experimental studies suggest a role for increased levels of inflammatory cytokines such as tumour necrosis factor- α and interleukin-6 (1, 21).

The early detection of the development of preeclampsia is important. One method is to investigate the amount of albumin in the urine. Urinary albumin excretion $> 300\text{-mg}/24\text{ h}$ is classified as overt albuminuria and preeclampsia. Albumin excretion in the range $30\text{-}300\text{-mg}/24\text{-h}$ is defined as microalbuminuria and is considered pathological (22, 23). Therefore, repeated urine analyses screening for microalbuminuria is part of standard antenatal care (24). The dipstick technique has been used, but in the 1960s, new assay techniques allowed the detection of low concentrations of urinary albumin excretion. In the Saint Vincent declaration on diabetic nephropathy (25), the 24-hour urine collection was recommended as the gold standard when screening for microalbuminuria.

Parturition

Pregnancy ends at parturition with the delivery of the baby. Labour involves a series of events occurring in a strict order. During parturition, the demand on the regulatory systems further increases. Labour implies physical work, which may be prolonged, pain, which may be severe, and anxiety. Therefore, different methods for accelerating delivery have been developed and are commonly practiced, along with pharmacological and non-pharmacological methods for pain relief. The methods are not universally beneficial and may cause adverse effects on the maternal body and the foetus, and disturbances to the regulation of e.g. uterine contractions, blood pressure, fluid balance, and placental function.

Parturition affects almost every organ system of the body, especially the reproductive system and its hormonal regulation. The cardiovascular system reverts from a high output - low resistance system to a normal non pregnant-state. In a similar way, the fluid balance shifts from accumulating water and electrolytes to excretion.

During pregnancy, large amounts of progesterone and estradiol are synthesized in the placenta and the concentration of estradiol further increase during labour. The high plasma progesterone production is maintained. After delivery of the placenta, the levels of progesterone and estradiol drop sharply and consequently their inhibition on the prolactin secretion decreases. Increasing secretion of prolactin stimulates lactogenesis.

Labour and delivery are generally considered stressful to both mother and foetus. On the maternal side, the stress may be partly due to fear, anxiety, and physical work. Most women experience pain, which may be severe, and anxiety. For many women in western society, parturition may be the first time for encountering these qualities of life. Each of these elements cause increased adenocortical activity (26, 27).

Plasma glucose increases during normal parturition (28-30), due to the combined affects of cortisol, epinenephine, and norepinephrine. Labour is associated with a marked increase in glucose utilisation and production. Furthermore, the increase of hepatic glucose production is favoured by an increase in glucagon, catecholamines and cortisol (31): anxiety and discomfort lead to increase in blood sugar concentration.

Phases of parturition

Delivery often starts with irregular uterine contractions, the latent phase, which may last for several hours. The first stage of labour is established when the contractions become regular and painful and there is a clear and

progressive cervical dilatation, usually about 3-4 cm/h. The length of the first stage is influenced by many factors, including parity and varies between women. The average length of the first stage in first time labouring woman (primipara) is about 8 hours, with large individual variation, and about 5 hours in subsequent parturitions (pluripara, multipara) (32-34). The second stage refers to the interval between full cervical dilatation and delivery of the infant. Uterine activity increases progressively during delivery and the second stage of labour is characterised by strong uterine contractions and the bearing-down or pushing efforts of the baby. The duration of the second stage in primipara is about one hour and less than half an hour in multipara (32, 35, 36). The third stage of labour denotes the interval between the delivery of the infant to the detachment and expulsion of the placenta and the deciduous membranes. The duration of the third stage is commonly about 5-10 minutes.

Dystocia [Greek: dys = difficult, tocos = labour] is a common complication of labour and may be caused by insufficient uterine contractions, unyielding uterine cervix, malpresentation, and foeto-pelvine disproportion (37). According to Swedish ICD-10 classification, a slow cervical opening rate is diagnosed as dystocia if cervical dilatation is < 1 cm/h (38). The World Health Organisation (WHO) defines prolongation during parturition as a cervical dilatation rate of less than 1 cm/h for a minimum of 4 hours (39).

Aftercare

There is a new turbulent period both psychologically and physiologically directly after delivery of the infant and the subsequent few hours: this period is called “aftercare” in this thesis. After delivery of the baby, the placenta is detached, often within minutes, and the secretion of placental hormones into the maternal circulation stops. The homeostasis of the pregnant maternal body has to change into the state of lactation or revert to the non-gravid state, if the mother is not nursing. Estrogens and progesterone from the placenta no longer inhibit the effect of prolactin on the milk-producing cells in the mammary glands and milk production starts.

In Sweden, when the child is born the procedure is to put the baby on the mother’s chest, skin-to-skin, and to encourage the mother to breastfeed. The child tries to reach the nipples. During this time, the placenta is detached and any ruptures are sewn. After approximately two hours, the baby is weighed and measured. The mother’s blood pressure is measured, the uterus palpated, the amount of bleeding checked, and the woman is encouraged to urinate. Thereafter, a sandwich and tea or coffee is served.

Puerperium

The puerperium is the period when all physiological systems have to adapt to a state of lactation or to revert to the state of non-pregnancy. When the placenta is detached and the inhibitory actions of the placental hormones have disappeared, milk production starts. Growth hormone, ACTH (acting via cortisol), thyrotropin (acting via the thyroid hormones), prolactin from the hypophysis, and insulin are necessary for fully developed milk synthesis. Each time the child suckles, a vagal reflex is initiated that inhibits dopamine release in the hypothalamus, and more prolactin is released. This maintains milk production. Each time the baby suckles, oxytocin is released and the milk down reflex appears to function in women as in other mammals. Although there is much information on the systemic cardiovascular and fluid regulatory system during pregnancy, less attention is given to the mother after parturition. One problem with reviewing the literature is that it is not always stated whether the neonate suckled or not.

Blood flow to the mammary glands increases during pregnancy along with the first development of the milk-secreting cells. After parturition, part of the blood previously supplying the foeto-placental unit is redirected to the breasts. All substrates and the water have to be supplied via the blood to the milk. Thus, intake of water and nutrients must increase and the increased metabolism leads to increased output of waste products.

Aims

Paper I

To investigate if the urinary albumin - to- creatinine ratio in spot samples could be a complement to the dipstick method and an alternative to 24-h urine collections during pregnancy.

To evaluate if the method would give reliable results in women with pre-eclampsia

Paper II

To investigate associations between plasma oxytocin and vasopressin concentrations and renal water and sodium excretion during normal pregnancy, in comparison to gestational hypertension.

To investigate if changes in the levels of plasma progesterone, estradiol, and estriol differed in women who developed pregnancy-induced hypertension, compared with women who were normotensive throughout pregnancy.

Paper III

To investigate how concentrations of estradiol, progesterone, oxytocin, cortisol, and glucose in the blood differed before and in the nearest hours after delivery, and how they were affected by treatment.

Paper IV

To investigate if treatment with oxytocin and opioids affected fluid balance during the different stages of labour, and if disturbances resulted in compensatory mechanisms during the 27 h postpartum.

Materials and Methods

Study populations

Two prospective longitudinal open trials were conducted. The first study took place at six urban antenatal clinics in Uppsala and Örnköldsvik, and one high-risk antenatal clinic at the University Hospital, Uppsala, Sweden (Papers I and II). The second study involved antenatal clinics in Katrineholm and Eskilstuna, and the delivery and maternity wards in Eskilstuna, Sweden (Papers III and IV).

In Papers I and II, the women were recruited when they visited the antenatal clinic in the 12th, 24th, and 36th weeks of pregnancy. In paper I, 65 women were included, of which 41 were normotensive and 34 were hypertensive. The same women were studied in Paper II, but eight were excluded as they were treated with antihypertensive drugs. For other exclusion criteria, see Papers I and II.

Evaluation of the blood pressure data and urine albumin excretion/24 h revealed that 37 women were normotensive throughout pregnancy and had only traces of albumin in the urine (7 ± 1 mg/24 h): they were designated normotensive women. Twenty women had elevated blood pressure in week 36. Fifteen of these had only traces in the urine (13 ± 2 mg/24 h) and were designated women with gestational hypertension. Six of the fifteen women were recruited to the study in week 12 and blood and urine sampling was possible throughout the study. The other nine women with gestational hypertension were recruited in weeks 24 or week 36 and were sampled as soon as they entered the study. The five remaining hypertensive women, recruited in week 36, had microalbuminuria (207 ± 40 mg/24 h): they were considered as having mild preeclampsia.

In Papers III and IV, the participants were healthy women with normal singleton pregnancies and who attended antenatal clinics in Eskilstuna. Sixty-six women consented to participate. Two women left early, three were delivered by caesarean section, and too few blood-samples were obtained from ten women. Thus, fifty-one women were included in the analyses.

Through evaluation of the partograms (40), women were grouped into three categories: normal, fast, and slow labour. Those, whose cervix had opened at a rate of 1-5 cm per hour were considered as having normal progress of labour, women with a opening rate of ≥ 5 cm/h were considered as having fast labour, and those with a progress of < 1 cm/h or no progress at all for more than two hours had slow labour.

Ethics

The first two studies were approved by the ethic committee in Uppsala and Umeå (Papers I and II), and the second in Stockholm (Papers III and IV). All women participating in the studies gave their informed verbal and written consent before inclusion.

Study designs

Papers I and II

At each visit to the antenatal clinics, the women were weighed, arterial blood pressure was measured, and blood samples were taken, always between 8.00 and 12.00 h. The women were asked to collect all urine during 24 hours, the volume was measured, the urine well mixed and samples were taken and kept frozen until analysis.

Papers III and IV

Blood and urine samples were taken before and after delivery. The blood and urine sampling were planned according the schedule: latency phase (sample 1), early in the 1st stage (sample 2), at the onset of the 2nd stage (sample 3), at aftercare (sample 4), and 6 hours (sample 5), 12 hours (sample 6), and 24 hours (sample 7) after the sample taken at aftercare.

The aftercare sample was taken immediately before the mother and child left the delivery ward and moved to the maternity ward. The time was recorded and a stopwatch started: the samples were collected 6-, 12- and 24-hours after sample 4. The mean time between delivery and sample 4 was 165 minutes, and the sampling time was adjusted accordingly, which was averaged to three hours after delivery. The women were asked to urinate at the same time as the blood sample was taken, and to store urine between samplings. The urine was mixed carefully before storage.

Collection of plasma and urine samples

Blood samples were collected from an antecubital vein into two 7 ml vacutainer tubes (Papers I and II) or two 10 ml vacutainer tubes (Papers III and IV): one tube was a serum tube and one tube contained K_3 - EDTA and aprotinin. The EDTA-tube was immediately put on ice, and care was taken to keep the sample cool until the plasma was transferred to a deep freezer (-70°C).

Urine was collected for 24 hours (Papers I and II). In Papers III and IV, the urine collections were coordinated with blood sampling. After collection, the volume was measured, and samples were well mixed. All plasma, serum, and urine samples were kept frozen at -70°C until analysis.

Analyses of blood and urine

All analyses were by validated methods and detailed descriptions are given in each paper. Some analytical methods were modified over the years of practical work for this thesis.

In Paper II, radioimmunoassays were used for the analyses of cortisol, estradiol, estriol, progesterone, and oxytocin. By the time the samples in the later studies were analysed, the laboratories had changed to enzyme-linked immuno-assay (EIA). The oxytocin analysis was validated in the laboratory at SLU, and the others at the University Hospital in Uppsala. No major differences between the methods were determined as regards the results. Vasopressin was analysed with radioimmunoassays (RIA) (Papers II - IV).

Pain relief treatment

During parturition, different methods of pain relief, both non-pharmacological and pharmacological, were used (Papers III and IV). In addition, the women were given analgesic drugs either as intramuscular injections of morphine or as epidural (EDA) injections of bupivacain and sufentanil (Table 2, in Papers III and IV). About one hour before the epidural injection, an intravenous infusion of Ringer-acetate (Fresenius Kabi AB, Uppsala, Sweden) was started and the women received 1000 ml in total during labour. Some women preferred tablets and took codeine + paracetamol.

Treatment of weak labour contractions

Intravenous infusion of oxytocin is the routine method for stimulating uterine contraction during labour. The aim is to achieve 2-3 contractions per 10 minutes, with each contraction lasting >40 sec (33-35). The period of aug-

mentation should be limited to four hours, unless there is progress, but can be continued up to six to eight hours, as long as there is evidence of progress (36).

Continuous and pulsatile infusions of oxytocin were given to women with weak uterine contractions and slow progress of labour (Papers III and IV). The concentration of the oxytocin infusion was 10 mU/ml, *i.e.* 10 IU of oxytocin was dissolved in 1000 ml 5% glucose. The continuous infusion started at an infusion rate of 15 ml/h. The rate was doubled every 30 minutes *i.e.* 15-, 30-, 60-, and 120-ml/min until the desired frequency of 3-5 uterine contractions per 10 minutes was reached. The maximum infusion rate was 120 ml/h. If contractions became too frequent, then the infusion rate was decreased. If the contractions ceased, despite ongoing oxytocin infusion, the infusion was stopped and started again later.

As a safeguard, the pulsatile infusion started from a much lower level with one pulse (injection) of 0.2 ml every 6.7 min, *i.e.* 9 pulses per hour corresponding to about 1.8 ml/h. If necessary, and if tolerated by the women (41), the pulse volume was increased every 30 minutes so that the infusion rates corresponded to 1.8-, 3.7-, 7.5-, 15-, 30-, 60-, and 120-ml/h (Octapump Injection System 1, Octagon, Uppsala, Sweden). An injection of oxytocin (10-30 IU) was given to about half of the participants after the child was born in order to stimulate the detachment of the placenta and to prevent major bleeding (Table 1).

Table 1. Number of patients in the fast, normal, and slow groups treated with oxytocin and different types of pharmacological pain relief. The treatments were given in the latency phase (L), early in stage 1 (SE), or at onset of stage 2 (OS), and postpartum (PP). (Papers III and IV).

Group	Analgesia		Oxytocin		
	EDA	Opioids i.m. or per os	(L,SE,OS)	Response	PP
Fast (n=10)	0	2			6
Normal (n=31)	7	13	7	6/7	14
Slow (n=10)	8	3	7	6/7	5

Statistical analyses

For analysis of the data, the Statistical Package for Social Sciences (SPSS, Windows, Copyright © SPSS Inc., 2004 – 2007) was used.

For comparisons within groups, the repeated measurement analysis of variance (procedure MIXED, SAS software, © 2002-2003 by SAS Institute Inc., Cary, NC, USA) was used (Papers III and IV).

Results

The basic characteristics of the women participating in the studies are summarised in the text in Paper II and in Table 1 in Papers I, III and IV.

In Papers I and II, one group of women were studied during pregnancy, and in Papers III and IV, another group of women were studied during parturition and the first 27 hours after parturition. Fluid balance during pregnancy and lactation will be presented first, then the relation of placental estrogens and progesterone to fluid balance. Finally, some aspects of the stress involved in parturition will be described.

Fluid balance during pregnancy and parturition

Arterial blood pressure increased in week 12 in some women and continued to be elevated throughout pregnancy (Paper II). The methods evaluated in Paper I determine the excretion of albumin in the urine and the albumin concentration remained low in the hypertensive group. Their fluid balance was compared with the normotensive women and no differences in plasma and urine osmolalities or urinary sodium excretion were found. The hypertensive women will not be discussed further, but the group of normotensive women will be discussed together with the women studied in Paper IV.

Normotensive women (Paper II and all women Paper IV)

During pregnancy, the mean plasma osmolality was between 282 – 285 mosm/kg (Paper II). The urine was concentrated and free water clearance was negative despite low plasma osmolality (Paper II). Plasma vasopressin concentration was low, but the plasma oxytocin concentration increased during pregnancy (Figure 1).

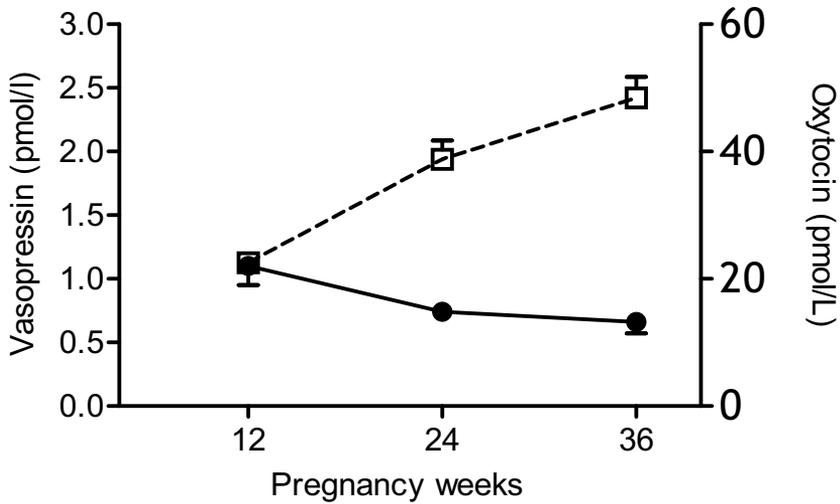


Figure 1. Plasma vasopressin (filled circles) and oxytocin (open squares) concentrations in normotensive women during pregnancy. Modified from Figure 1 in Paper II. Values are means \pm SEM.

Osmolality continued to be low during parturition and the first hours postpartum (Table 2), but increased 27 hours postpartum. This corresponded to similar changes in plasma sodium concentration (Table 2). Similar to during pregnancy, the urine osmolality was generally higher than plasma osmolality during parturition before delivery (Figure 2).

Table 2. Plasma electrolyte and hormone concentrations in all participants ($n = 51$). Modified from Table 4, Paper IV.

Event	Na conc. (mmol/L)	Osmolality (mosm/kg)	Vasopressin (pmol/L)	Oxytocin (pmol/L)
Arrival	142 ± 1 (28)	284 ± 1	0.37 ± 0.05 (30)	30 ± 2 (26)
Early stage 1	141 ± 1 (28)	284 ± 1	0.48 ± 0.07 (40)	29 ± 2 (33)
Onset stage 2	142 ± 1 (28)	285 ± 2	0.48 ± 0.05 (33)	28 ± 2 (30)
Aftercare	142 ± 1 (46)	288 ± 2	0.55 ± 0.09 (48)	36 ± 5 (50)
P + 9 h	141 ± 1 (45)	287 ± 3	0.44 ± 0.07 (49)	26 ± 1 (50)
P + 15h	143 ± 1 (45)	285 ± 1	0.38 ± 0.04 (50)	29 ± 2 (49)
P + 27 h	144 ± 1 (48)	290 ± 2	0.41 ± 0.04 (50)	28 ± 1 (50)

Values are mean ± (SEM). Numbers within parenthesis are number of patients in that sample.

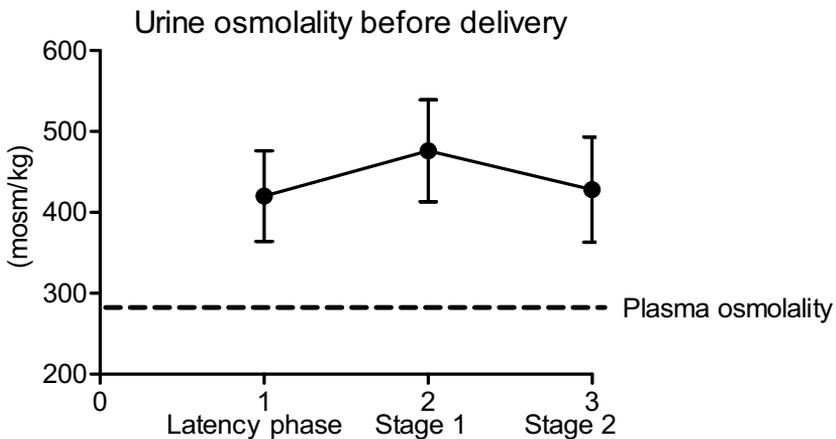


Figure 2. Urine osmolality in pregnant women ($n = 51$) before delivery. Values are means ± SEM. Reproduced from Paper IV.

These results indicated that normotensive pregnant women had low plasma osmolality throughout the pregnancy from week 12. During parturition, the women had the same low plasma osmolality in the latency phase, which remained throughout parturition, but started to increase 27 hours after delivery.

However, detailed data analysis on osmolality in the second study group revealed individual differences before delivery. Three groups were defined on the basis of cervical opening rates. Thirty-one women had a cervical opening rate between 1-5 cm/h, which is considered normal, and these constituted the normal group. Ten women had an opening rate >5cm and constituted the fast group, and ten women had an opening rate <1 cm or arrested progress and constituted the slow group. The differences were related to the treatment given to the participants (Table 2).

Plasma Sodium (Na) concentration decreased in stages 1 and 2 in the slow group, remained unchanged in the normal group, and was comparatively high in the fast group (Figure 3). After delivery and 27 hours after partus, plasma Na concentration slowly increased and there was no longer any difference between groups.

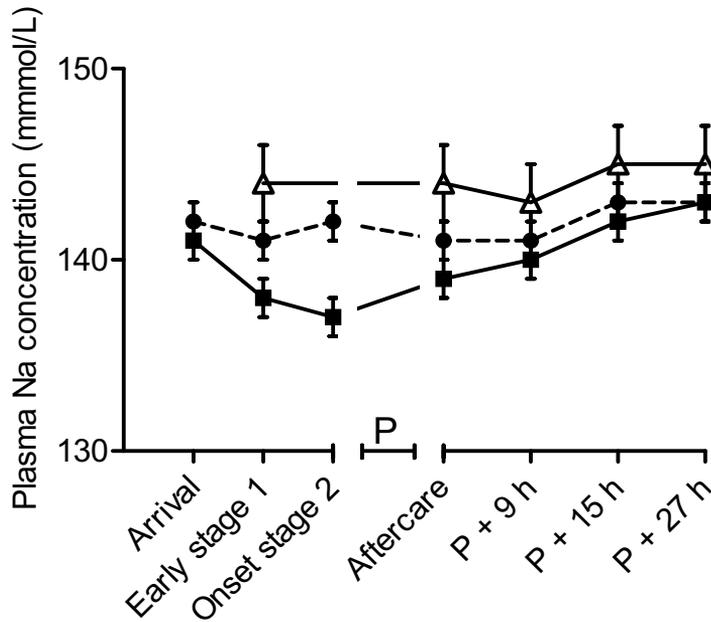


Figure 3. Plasma Na concentration before and after parturition (P) in women (normal group, dots, hatched line), women with >5cm opening rate (fast group, open triangles), and women with <1 cm opening rate or arrested progress (slow group, filled squares). Onset of stage 2, $p < 0.05$ normal vs. slow group; Aftercare, $p < 0.05$ fast vs. normal and slow groups. Values are mean \pm (SEM).

Before parturition, the women had difficulty urinating and some had to be catheterised. In the fast group, there was no time to collect most of the urine samples, but the volume was small in the samples collected (Paper IV). At aftercare, urine flow increased and continued to rise until 15 hours after parturition.

Urine osmolality was concentrated before delivery (Figure 4), but decreased after delivery, in the slow and the fast group osmolality decreased to below plasma osmolality, and, in the normal group, osmolality decreased to just above plasma osmolality (Figure 2).

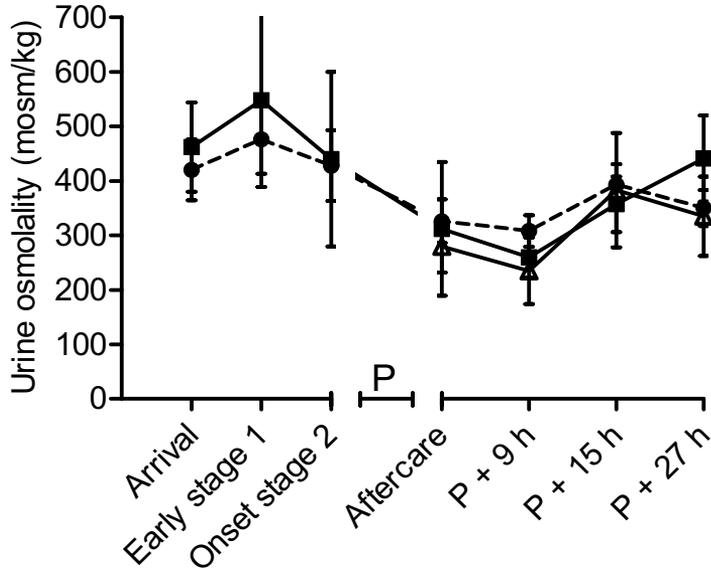


Figure 4. Urine osmolality before parturition (P) in the normal and slow groups (missed in the fast group) and in all three groups after parturition. For explanation of symbols, see legend in Figure 3. $p < 0.05$ early stage 1 vs. aftercare and 9 hours after parturition in both the normal and slow groups. Values are mean \pm (SEM). Reproduced from Paper IV.

Glomerular filtration rate (GFR) measured by the Cystatin C method was lower in all groups before delivery than at aftercare ($P < 0.001$). After parturition, GFR increased in the fast and slow groups to the same level as the normal group (Paper IV).

Plasma oxytocin concentrations before, during, and after delivery

Oxytocin might play many roles in the body, as demonstrated by the work presented here. This peptide could be involved in fluid balance, although, the main targets for oxytocin are the uterus and the mammary glands. Plasma oxytocin concentration was higher in week 36 than at the beginning of parturition (Paper II) and did not change during the phases of labour: the highest value was during aftercare in the normal group, when it had increased from 29 ± 2 pmol/l at stage 2 to $40 \pm$ pmol/L. The values did not change in the other groups (Paper III).

Seven women in the normal group and seven women in the slow group were treated with oxytocin. Five women in the slow group received oxytocin as a pulsatile infusion and two as a continuous infusion, this was vice versa in the normal group. The total dose of oxytocin necessary to affect labour was 0.33 ± 0.17 IU (range 0.01-1.18) when given as a pulsatile infusion and 2.18 ± 0.48 IU (range 0.36-3.73) when given as a continuous infusion ($p < 0.05$). One woman in the normal group was treated with amniotomy, as she did not respond, and one woman in the slow group was treated with vacuum, as she did not respond.

Twenty-five women were given 10–30 IU oxytocin as prophylaxis postpartum (PP) to prevent bleeding (Table 1). There was no difference in time for placenta detachment or in blood loss in women given PP injections of oxytocin. There was no difference in oxytocin concentration in blood samples between women treated with oxytocin and untreated women.

Serum cortisol and glucose concentrations before, during, and after delivery

Parturition is a stressful event and cortisol and glucose were measured to provide an indication of the degree of stress. The cortisol concentration was high on arrival at the hospital and increased in stage 1 in all groups. Cortical concentration remained high during aftercare in all groups, with the highest value in the slow group, and dropped rapidly thereafter (Table 4).

Table 4. Blood serum cortisol concentrations in women with normal ($n = 31$), slow ($n = 10$), and fast labours ($n = 10$). Number of samples were: normal group ($n = 20$ before delivery, $n = 28$ PP); fast group ($n = 2-5$ before delivery, $n = 9$ PP); slow group ($n = 4-8$ before delivery, $n = 10$ after delivery)

Event	Normal	Fast	Slow
Arrival	987 ± 120	1093 ($n = 2$)	1075 ± 318
Early stage 1	1275 ± 92	1532 ± 166	1480 ± 183
Onset stage 2	1596 ± 144	1510($n = 2$)	1514 ± 85
Parturition			
Aftercare	1183 ± 53	1254 ± 214	1438 ± 135
P + 9 h	680 ± 47	756 ± 146	659 ± 172
P + 15h	792 ± 49	778 ± 70	671 ± 70
P + 27 h	539 ± 38	527 ± 68	458 ± 64

Values are means ± SEM. $p < 0.05$ normal vs. slow group at aftercare.

Serum glucose concentration was 6.0 ± 0.3 mmol/L in the normal group, 5.6 ± 0.3 in the slow group, and 5.8 ± 0.2 mmol/L in the fast group during pregnancy week 12, with no differences throughout pregnancy (data collected from the antenatal clinics). On arrival at the hospital, the values were in the same range or even higher in all groups before delivery and further increased at aftercare ($p < 0.05$ vs. all samples before delivery and post aftercare). Within the normal group, the glucose concentration increased from 7.0 ± 0.4 mmol/L in the latency phase to 8.6 ± 0.7 mmol/L at onset of stage 2 ($p < 0.05$), and then to 12.1 ± 0.6 mmol/L at aftercare ($p < 0.05$) (Figure 5).

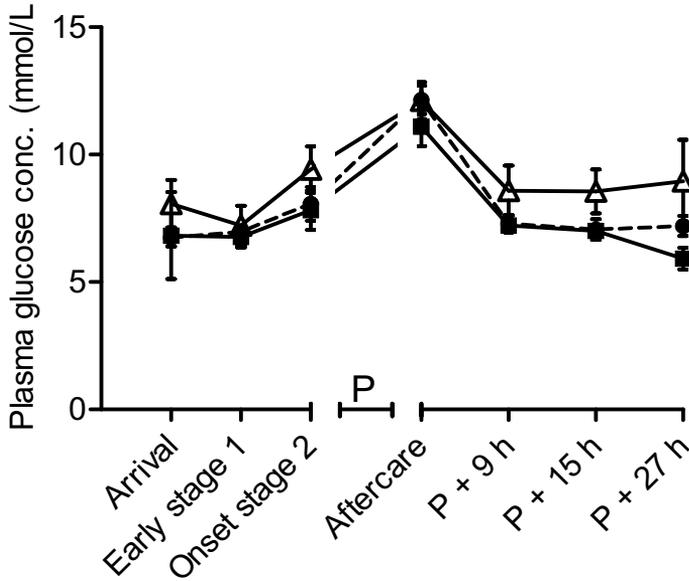


Figure 5. Plasma glucose concentrations in women with normal (●, $n = 31$), slow (■, $n = 10$), and fast labours (Δ, $n = 10$). For number of samples in each group, see Table 4. Values are means \pm SEM. $p < 0.05$ arrival vs. stage 2; aftercare vs. samples before parturition and after aftercare.

Estradiol and progesterone during pregnancy and parturition

Plasma estradiol and progesterone concentrations increased as expected from week 12 to week 36 (Paper II), and estradiol further increased before delivery (Paper III) and was higher in the normal group (111 ± 8 nmol/L) than in the slow group (72 ± 9 nmol/L; $p < 0.05$). At aftercare, the mean estradiol level was still elevated in the slow group ($p = 0.056$ vs. the normal group), but the individual variations were large (Table 5). Serum progesterone concentration was elevated during labour and decreased after delivery. There was no difference between groups in progesterone concentration (Table 5).

Table 5. Serum concentrations of estradiol and progesterone during parturition in women with normal ($n = 31$), slow ($n = 10$), and fast labours ($n = 10$). At arrival, the women were in latency phase. Number of samples were: normal group ($n = 20$ before delivery, $n = 28$ PP); fast group ($n = 2 - 5$ before delivery, $n = 9$ PP); slow group ($n = 4-8$ before delivery, $n = 10$ after delivery). Reproduced from Paper III.

Event	Normal	Fast	Slow
<i>Estradiol nmol/L</i>			
Arrival	111 ± 8	66 ($n = 2$)	68 ± 15
Early stage 1	114 ± 7	113 ± 9	112 ± 21
Onset stage 2	119 ± 8	145 ($n = 2$)	95 ± 18
Parturition			
Aftercare	10 ± 1	11 ± 2	25 ± 15
P + 9 h	4 ± 0.4	3 ± 3	21 ± 18
P + 15h	2 ± 0.3	1 ± 1	4 ± 2
P + 27 h	1 ± 0.2	1 ± 0.6	1 ± 0.5
<i>Progesterone nmol/L</i>			
Arrival	682 ± 45	565 ($n = 2$)	601 ± 112
Early stage 1	615 ± 41	547 ± 106	572 ± 110
Onset of Stage 2	571 ± 36	962 ($n = 2$)	478 ± 107
Parturition			
Aftercare	158 ± 10	150 ± 18	195 ± 50
P + 9 h	121 ± 8	112 ± 17	129 ± 16
P + 15h	76 ± 6	79 ± 16	83 ± 21
P + 27 h	44 ± 4	46 ± 10	51 ± 11

Note: Values are expressed as means and SEM. Estradiol at arrival (latency phase), $p < 0.05$ normal vs. slow groups

Discussion

In normal human pregnancy, total body water increases by 6-8 litres and plasma osmolality decreases about 10 mosm/kg below non-pregnant levels. The thresholds for thirst and vasopressin release decrease during the first trimester (1, 2). In Paper II, both the plasma osmolality and the vasopressin concentration were low, but in a majority of samples, the urine was concentrated. This confirmed earlier findings (3) that women can regulate fluid balance at a lower set point during pregnancy. This was the case with women in both the normotensive group and the women with pregnancy-induced hypertension, their urinary flow, osmolality, and renal Na excretion did not differ. Elevated blood pressure was not treated and the women gave birth at the normal time. Elevation of arterial blood pressure can occur during pregnancy with no large effects on fluid balance, but if blood pressure is combined with high urinary excretion of albumin, the situation changes, as indicated by the women with mild preeclampsia in Paper II.

In the first two trimesters, regulation appears normal around the new set point, but during the last trimester, the water load is not easily excreted (3) and the release of vasopressin in response to hypertonic NaCl solutions is attenuated (4). Vasopressin levels reached the lowest level in the third trimester (Paper II), but there was no decrease in urine osmolality. At the same time, plasma oxytocin concentration increased. Oxytocin is an antidiuretic during pregnancy (12, 13, 42), and there is an indication oxytocin assists vasopressin in concentrating urine.

This does not mean oxytocin is regulated according to the demands of fluid balance in the body. In response to osmotic stimuli, vasopressin and oxytocin can be released together from the neurohypophysis in the rat during pregnancy and lactation (43) and in the goat during lactation (44), although an osmotic regulation of oxytocin in humans is not proven (45). Instead, it is suggested oxytocin acts in the vasopressin-2 receptors in the kidneys to maintain urine concentration before parturition, regardless of changes in blood plasma osmolality and volume.

At the onset of labour, the condition can be characterised as hypervolemic hyponatremia with low tolerance to water loading or hypertonic solutions. When the results from the whole group of women were summarised, there was no apparent difference in plasma and urine osmolality before and 27

hours after delivery. These values did not reflect changes during parturition. Women with uncomplicated and fast progress of labour had a plasma Na concentration close to non-gravid levels (Paper IV). In contrast, the group with slow progress of labour, who were given fluid administration with hypotonic solutions, developed hyponatremia. These results supported the work of Moen et al (46) where women with prolonged parturition had hyponatremia.

Both pulsatile and continuous infusion of oxytocin were established as effective in the treatment of slow progress of labour, and lower amounts of oxytocin were required to affect delivery when administered as a pulsatile infusion. Treatment with hypotonic solutions with or without oxytocin (Papers III and IV) did not necessarily lead to hypovolemia, as 12 women in the normal group were treated and presented no change in plasma Na concentration. One difference between the different groups could have been that the latter women were treated closer to parturition and, therefore, given less fluid. They gave birth within the same period as the other women in the normal group.

The slow group differed from the other groups in other aspects than just fluid balance. Although the number of women was small, the observations are interesting. In the latency phase, the slow group had lower serum estradiol concentration than the normal group. After delivery, when the placenta had detached and the production of estradiol ceased, general serum estradiol concentration decreased, but individual differences remained large during aftercare and up to nine hours after delivery. At aftercare, the slow group had the highest serum cortisol concentration, indicating stress level was high: these findings present the opportunity for further study in a larger group of women.

Before delivery, the maternal organism appeared to maintain an enlarged volume in the extracellular space, even if it meant dilution of the plasma. The regulatory mechanisms that keep plasma osmolality within narrow limits in the non-gravid state (47) did not function in the usual manner before delivery and during the aftercare period.

At aftercare, urine flow increased and had further increased in the sample taken nine hours after delivery. The women with both fast and slow labour excreted diluted urine during this time (Paper IV). However, at the same time, the plasma Na concentration increased in the slow group but not in the fast group: the plasma vasopressin concentration remained low. Thus, there was still no relation between plasma and urine osmolality, but, about a day after delivery, there were no longer any difference in fluid balance parameters among the three groups. This indicated that at this time, the osmoregulatory system started to function in the same manner as before pregnancy.

Before delivery, plasma oxytocin concentration did not vary among the groups; supporting that centrally released oxytocin is probably not important for uterine contractions during labour in humans (16). After delivery, oxytocin appears to act as in other mammals, in that circulating oxytocin is involved in placenta detachment, myometrial contractions, vasoconstriction in the uterus, and for milk let down (48). Plasma oxytocin concentration was highest in the normal group at aftercare (Paper III), but due to the longer intervals between the blood samples, the pulses of high oxytocin concentration might have been missed in the other groups.

The period directly after delivery, which is aftercare in this thesis, involves the transition from pregnancy to lactation and is a challenge for the maternal body. Placental hormones suddenly disappear, a lot of pain persists, and mother and child meet for the first time. Both the physiological and the psychological systems have to readjust to this new situation. The enlarged extra cellular plasma volume of pregnancy diminishes, but lactation involves increased blood supply to the mammary glands and increased demands for nutrients and water for milk production. All babies stayed with their mothers for the first hours after birth and, except for two, all women nursed: this time resembles a period of calm after the dramatic events during delivery. However, at aftercare, the serum cortisol level remained elevated and the glucose concentration reached very high levels (Paper III): this was probably due to a combination of stress, metabolic changes, and start of lactation

In conclusion, fluid balance is not regulated according to the usual sensitive osmotic and volumetric influence on vasopressin release from the neurohypophysis. Although direct evidence is lacking, changes in the regulation of fluid balance were coordinated in time with the initiation and termination of placental production of estradiol and progesterone. Parturition involves a change from one demanding condition, pregnancy, to another, lactation. The hours directly after delivery are a turbulent period involving considerable stress.

Conclusions

- The increasing oxytocin concentration from pregnancy week 12 to week 36 may have assisted vasopressin in concentrating the urine throughout pregnancy.
- There was no difference between groups in urine flow and urine osmolality was above plasma osmolality in the majority of samples.
- Renal sodium excretion did not change between the pregnancy weeks and there was no difference between groups, indicating that changes in plasma concentrations of vasopressin, oxytocin, estradiol, or progesterone did not influence renal sodium excretion during pregnancy.
- Both pulsatile and continuous oxytocin was effective in the treatment of slow progress of labour, but less oxytocin was needed to affect delivery when given as a pulsatile infusion.
- Serum cortisol and glucose concentrations were high during labour and aftercare, probably due to a combination of stress, metabolic changes, and start of lactation.
- Estradiol and progesterone concentrations fell, as expected, at aftercare and nursing did not present any problems, according to the reports by the midwives.
- Plasma vasopressin concentration was low during parturition, but the urine was concentrated when plasma Na concentration decreased during long labour and treatments with oxytocin and analgetics. Increased volumes of diluted urine were excreted postpartum in all groups.

- The measurement of the albumin/creatinine ratio was a convenient and useful alternative to 24-h urine collection for detecting albuminuria in pregnancy.

Summary in Swedish/ Svensk sammanfattning

Under mänsklighetens historia har kvinnor fött barn och i de flesta fall så går det bra. Vi ser graviditet, barnafödande och amning som en naturlig del i vår tillvaro.

Det är sedan tidigare känt att kvinnan genomgår tydliga fysiologiska förändringar under graviditet, förlossning och perioden efter barnafödandet vilket också inkluderar övergången till amning.

För att förstå dessa perioder bättre ur ett fysiologiskt perspektiv så har vi studerat 51 kvinnor och deras hormon- och vätskebalans under graviditeten, så också i olika faser under förlossningen och slutligen fram till 27 timmar efter förlossning.

Steroidhormonerna estradiol, progesteron och kortisol, samt peptidhormonerna oxytocin och vasopressin har studerats i relation till salt och vätskebalans under graviditet, förlossning och 27 timmar efter förlossning.

I avhandlingen bekräftas att vätskebalansen regleras väsentligt annorlunda under graviditet och förlossning jämfört med det icke gravida tillståndet. Vasopressin som normalt koncentrerar urinen visade låga värden, kvinnorna hade ökad blodvolym, och blodplasman var något utspädd och likväl koncentrerade kvinnorna urinen. Eftersom oxytocin också kan koncentrera urinen så föreslogs att denna peptid åstadkom den koncentrerade urinen utan hänsyn till de sedvanliga regulatoriska faktorerna.

Utdragna förlossningar

De kvinnor som hade utdragna förlossningar var alla behandlade med smärtlindring och de flesta också med oxytocin för att stimulera till värkarbete.

Oxytocin har länge använts till igångsättning vid värksvaghet. Idag används kontinuerlig infusion av oxytocin för att stimulera livmodern till kontraktioner när kvinnor inte kommer igång med värkarbete eller om värkarbetet avstannar. Pulsvis infusion av oxytocin jämfördes med kontinuerlig infusion och den behandlingen visade sig vara lika effektiv, men med en mindre mängd oxytocin. Att kunna minska den totala mängden oxytocin är viktigt

då höga koncentration av oxytocin i blodet är antidiuretiska, som nämnts ovan, och därmed späds blodet ut. Detta kan leda till nervösa störningar hos både mamma och barn.

Kvinnor som genomgår ett utdraget förlossningsarbete var inte bara avvikande genom att deras förlossningsarbete tog längre tid utan även genom att de hade lägre estradiolnivåer i blodet i början på förlossningsarbetet. Estradiol anses bidra till att oxytocinreceptroerna i livmodern ökar i antal alldeles före förlossningen och detta är en förutsättning för att värkarbetet skall komma igång. En ofullständig stimulering av oxytocinreceptorerna kan ha varit en orsak till de svaga värkarna som sågs i denna grupp kvinnor i studien.

Snabba förlossningar

Omvänt hade de kvinnor som inte använde sig av någon smärtlindring de snabbaste förlossningarna och de högsta nivåerna av natrium i plasma efter förlossning. Att föda barn har blivit jämfört med att springa ett maratonlopp och då också med rådet att mer intravenös vätska under förlossning behövs för att kompensera för förlusterna av vätskeförlusterna under arbete. Men det är ett observandum att de kvinnor som födde snabbt ökade urinflödet och övergick till en vattendiures tidigt efter förlossningen, vilket talar för att de inte led av vätskebrist. De snabba förlossningarna är korta och intensiva och kan snarare jämföras med att springa en mil jämfört med att springa ett maratonlopp.

Progesteron och estradiolnivåerna i serum försvann långsammare efter förlossningen hos kvinnor som genomgick utdragna förlossningar. Detta trots att deras moderkaka släppte lika snabbt som de med normala och snabba förlossningsförlopp. Att estradiol- och progesteronnivåerna sjunker är viktigt för att amningen ska komma igång eftersom framför allt progesteron hämmar det mjölkstimulerande hormonet prolaktin. När hämningen släpper så kan prolaktinet stimulera bröstet till mjölkproduktion.

Det finns ett fåtal studier gjorda under den första tiden efter förlossningen och det framgår inte alltid om kvinnan ammar eller inte vilket är av stor betydelse för vätskebalansen. För den kvinna som inte ammar, återgår de förändringarna i blod och urin som inträtt under graviditet och förlossning gradvis till de normala inom ca sex veckor. De kvinnor som ammar övergår till ett nytt tillstånd i vilket många av kroppens regleringssystem inklusive vätskebalans, blodcirkulation och kalciumomsättning ändras.

Koncentrationerna av kortisol och glukos i serum var höga under förlossning och omedelbart efter förlossningen, troligtvis på grund av stress, metaboliska förändringar och start av amning.

Denna avhandlingen i fysiologi, "Hormones and fluid balance during pregnancy, labor and post partum" har gett oss nya insikter om de stora förändringar i hormon- och vätskebalansen som äger rum direkt efter det att barnet fötts och moderkakan stötts ut. Då genomgår kvinnan ännu en förändringsfas men denna gång till en omställning i vätskebalansen för att producera mjölk och amma.

Forskningen har bedrivits vid kvinnokliniken och mödravårdscentraler i Mälarsjukhuset i Eskilstuna, Örnsköldsvik sjukhus och Uppsala Akademiska sjukhus, samt vid institutionen för Medicinsk cellbiologi enheten för integrativ fysiologi, Medicinska fakultetet, Uppsala universitet. Analyser har utförts vid Akademiska sjukhuset och vid institutionen för anatomi, fysiologi och biokemi vid fakulteten för vetinärmedicin och smådjursvetenskap, Statens lantbruksuniversitet, Uppsala.

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