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NOVEL ASPECTS ON OSMOLALITY AND PLASMA SODIUM DURING PREGNANCY AND LABOUR

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Cover page: detail from "Primavera" by Sandro Botticelli (1445-1510)

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Novel Aspects on Osmolality and Plasma Sodium during Pregnancy and Labour
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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fatti non foste a viver come bruti,

ma per seguir virtute e canoscenza

"you were not made to live like brutes or beasts,

but to pursue virtue and knowledge"

Dante Alighieri (1265-1321)

La Divina Commedia, Inferno XXVI; 119-120

ABSTRACT

This thesis was designed to study causes and effects of changes in plasma sodium and osmolality during pregnancy and labour.

The physiological changes of early pregnancy include reduction in plasma sodium and osmolality, as well as increased ventilation with reduced arterial pCO_2. These changes are usually considered due to progesterone. Some studies have however correlated these two events and found that reduction in osmolality and strong ion difference (SID, the difference between strong cations and anions) may predict respiratory changes in pregnant women. We hypothesised that changes in osmolality should influence ventilation also in non-pregnant women and men, and we therefore studied the ventilatory response to lowered and increased osmolality in healthy volunteers, ten men and nine women. Ingestion of water and intravenous infusion of hypertonic saline 3% caused osmolality to decrease and increase, respectively. SID and base excess decreased in both conditions, and a respiratory compensation was observed during water loading, but although the metabolic acidosis was more pronounced during salt loading, no respiratory compensation was observed. The principal influence of osmolality on ventilation could be inhibitory when osmolality is increased, but this inhibitory effect could cease at decreased osmolality.

The hyperventilation observed during pregnancy often exceeds the respiratory compensation observed in our study participants, but this remains to be explained.

We also studied the feto-maternal osmotic and electrolyte relationship, and contrary to the literature, we found that fetal plasma sodium and osmolality were higher than maternal levels. Our results indicated that the physiologic hyponatraemia of pregnancy caused both a compensatory respiratory alkalosis that favours removal of fetal CO_2, as well as an osmotic gradient that favours water transport to the fetus. This unifying explanation of maternal physiologic adaptation and feto-maternal relationship differs from the conventional explanatory model that considers the respiratory alkalosis primary, and the metabolic acidosis compensatory.

In addition to the physiological lowering of plasma sodium in the pregnant woman, hyponatraemia may develop during labour. We included 287 women during labour in a prospective observational study, and found that hyponatraemia was common following long lasting labour. Sixteen women (26 %) of those who received more than 2.5 liters of fluid during labour developed hyponatraemia ≤130mmol/L. Multivariate analysis revealed that hyponatraemia was significantly correlated to total fluid volume, but not to oxytocin or epidural

analgesia. All women consumed a similar hourly fluid volume of approximately 300 milliliter, but during long lasting labour, probably with an increased secretion of vasopressin, free water clearance was reduced, and hyponatraemia could develop.

Reduction in plasma sodium during labour also significantly correlated to instrumental delivery. We therefore studied the effect of hyponatraemia on human myometrium in an in vitro study. Hyponatraemia induced reversible changes with increased frequency of contractions and also of multiphasic contractions. These changes could indicate decreased myometrial contractility. In the second part of the study we found that initial multiphasic response to increasing doses of oxytocin was significantly more frequent in the hyponatraemic solution. These results indicate that hyponatraemia could be one of several factors leading to dystocia. Electrolyte free solutions should not be administered during labour, and a bedside registration of fluid consumption would be a simple preventive measure against hyponatraemia.

LIST OF SCIENTIFIC PAPERS

I. Vibeke Moen, Lars Brudin, Mats Rundgren, Lars Irestedt
    Osmolality and respiratory regulation in humans
    Respiratory compensation for hyperchloremic metabolic acidosis is absent
    following infusion of hypertonic saline in healthy volunteers

    Anesth Analg. 2014; 119: 956-64.

II. Vibeke Moen, Lars Brudin, Mats Rundgren, Lars Irestedt
     Hyponatraemia complicating labour. Rare or unrecognized?A prospective
     observational study

     BJOG 2009; 116: 552-61.

III. Vibeke Moen, Lars Brudin, Anette Ebberyd, Maria Sennström, Gunvor
      Ekman-Ordeberg, Mats Rundgren, Lars Irestedt
      Hyponatraemia reversibly affects human myometrial contractility
      An in vitro pilot study

      Submitted

IV. Vibeke Moen, Lars Brudin, Ivar Tjernberg, Mats Rundgren, Lars Irestedt
     Feto-maternal osmotic balance at term. A prospective observational study

     J Perinat Med 2017; aop

CONTENTS

LIST OF ABBREVIATIONS

ABL	Acid base laboratories
ADH	Antidiuretic hormone
ANCOVA	Analysis of covariance
ANG II	Angiotensin II
ANOVA	Analysis of variance
AP	Action potential
A-tot	Total weak non-volatile acids (mostly albumin)
AUC	Area under the curve
AVP	Arginine vasopressin
AVPase	Enzyme that degrades AVP
BE	Base excess
BMI	Body Mass Index (kg/m^2)
C-terminal	End with the atom C, as opposed to end with the atom N
DI	Diabetes Insipidus
ET	End tidal
G	Gauge, measure of needle size (higher G, smaller size)
HELLP	Syndrome of haemolysis, elevated liver enzymes, low platelets
ISE	Ion specific electrode
IU	International unit
mEq/L	Milliequivalent per liter
Mg	Milligram, 10^{-3} gram
Ml	Milliliter, 10^{-3} liter
µl	Microliter, 10^{-6} liter
Mmol	Millimol, 10^{-3} mole
mOsm	Milliosmole, 10^{-3} osmole
mU	Milliunit, 10^{-3} Unit
OT	Oxytocin
$PaCO_2$	Arterial partial pressure of CO_2

Pmol	Picomole, 10^{-12} mole
SD	Standard deviation
SIAD	Syndrome of inappropriate ADH secretion
SID	Strong ion difference
UA	Unmeasured anions
V1,V2,V3	Vasopressin receptors V1,V2,V3

INTRODUCTION

The physiological adaptation to pregnancy is often evident long before the growing womb reveals fetal presence. The florid appearance of the pregnant woman with glowing skin and rosy lips are caused by vasodilation and increased cardiac output (1). Other well known characteristics are morning sickness, and increased ventilation with lowered arterial pCO_2 ($PaCO_2$). All changes are often referred to as "progesterone induced" (1), however, recent studies indicate more complex explanations to these profound and reversible physiological adaptations to pregnancy.

The significant decrease in systemic vascular resistance and increased cardiac output are now believed to be induced by relaxin, a hormone produced by the corpus luteum (2). Relaxin is also believed to be responsible for the lowering of plasma osmolality (3), another characteristic of early pregnancy. Moreover, studies have found a correlation between reduced osmolality and increased ventilation (4,5).

In addition to the physiological hyponatraemia of pregnancy, a further lowering of plasma sodium may develop during labour (6,7). Observational studies and case reports have not infrequently described maternal and fetal hyponatraemia following labour (8-10). In more recent years voluntary overdrinking has replaced iatrogenic causes of hyponatraemia (7). Feto-maternal osmotic relationship is an important factor for water transport, however data reported in literature are scarce, and most often dated. One of our studies showed that plasma sodium reduction during labour correlated with instrumental delivery. Myometrial contractility involves complex interaction of ions but, to the best of my knowledge, no human study has addressed the possible impact of hyponatraemia.

1.1 BACKGROUND

The physiological adaptation to pregnancy involves literally every organ and system in the pregnant woman. This thesis was designed to study causes and effects of changes in plasma sodium and osmolality during pregnancy and labour. Below follows a description of the physiological changes that are of main interest for the topic of this thesis

1.1.1 Physiological changes of pregnancy. The role of relaxin

Significant physiological changes are evident in early stages of pregnancy, indeed, these changes are detectable already in the luteal phase of the menstrual cycle (4,5). Lowering of plasma osmolality and sodium, and also the osmotic threshold for thirst are detectable after ovulation. Water and sodium retention continues following conception causing mild

hyponatraemic hypervolaemia. Reduction in plasma osmolality reaches approximately 10 mOsm/kg mainly as a result of a decrease in plasma sodium by 3-5 mmol/L. By 12 weeks of gestation this adaptation has stabilised, and plasma osmolality remains low until after delivery (4,11).

Decrease in $PaCO_2$ is observed simultaneously with these early changes and progesterone is commonly considered responsible (1). However, some studies indicate that reduction of osmolality and strong ion difference (SID) may be the cause of increased ventilation (4,12).

Vasodilation, increased blood volume and cardiac output are other more well known changes that occur in early pregnancy (1). The increase in cardiac output together with renal vasodilation increases glomerular filtration rate with approximately 50 %. Blood pressure, particularly diastolic blood pressure, is reduced during pregnancy, and the response to vasopressors is attenuated (1).

The hormone relaxin, secreted from the corpus luteum, is now believed to initiate the process of metabolic and haemodynamic adjustments to pregnancy previously attributed to progesterone (2,13). Relaxin is a 53 amino acid peptide hormone characterised by a structure similar to insulin. Discovered in 1926 (14), relaxin was found to relax the symphysis in pregnant mares, hence the name.

The important role of relaxin for adaptation to pregnancy was later recognised (2). Relaxin plasma levels increase when pregnancy is established, reaching maximum levels at the end of the first trimester. Thereafter relaxin is present throughout the remaining gestation, but at lower levels.

Some researchers have considered that the systemic vasodilation leading to "underfilling" initiates water and sodium retention (12). However, studies in rodents showed comparable time-course of renal vasodilation and reduction in plasma osmolality (15). Recent studies also indicate a more complex mechanism, as relaxin affects the release of oxytocin and vasopressin by central stimulation (3,16,17). Animal studies show that osmosensors respond to circulating hypertonicity, angiotensin II (ANG II) and relaxin, and that relaxin has an effect similar to hypertonicity on the osmosensitive neurons in the hypothalamus (18).

1.2 OSMOLALITY, VASOPRESSIN, AND OXYTOCIN

Sodium and the corresponding anions are the main osmoles in extracellular fluid, and sodium concentration mainly reflects body water content. Extracellular osmolality can be determined by cryoscopy and may also be calculated by the formula

Osmolality (mOsm/kg) = (2[Na]mmol/L + [urea] mmol/L + [glucose]mmol/L) (19)

Reabsorption of water in the collecting ducts of the kidney is controlled by vasopressin, also known as the antidiuretic hormone (ADH), in turn regulated by plasma osmolality. Extracellular fluid volume is governed by the sodium homeostasis, and renal sodium excretion is regulated by the renin-angiotensin-aldosterone-axis.

Vasopressin and oxytocin (OT) are small neuropetides present in all mammals. Probable precursors, similar in structure and analogue in function, are present also in invertebrates and the origin of this signalling system dates back 600 million years (20). Vasopressin and OT probably originated by duplication of the ancestral vasotocin gene (21). The human vasopressin contains arginine, and is therefore often denominated arginine-vasopressin (AVP).

 OT and AVP differ only in two of nine amino acids, and both hormones are involved in a wide range of physiological processes including reproduction, renal water reabsorption, blood pressure control, modification of social behaviour, and neonatal adaptation. Half-time life of AVP and OT in plasma is short, around 4-20 minutes (22). Release of AVP is controlled by central osmoreceptors situated in areas in the hypothalamic region that are at least partly located outside the blood-brain barrier (23). Pain, stress, and fear are non-osmotic stimuli for AVP secretion. Hypovolaemia and hypotension are however the most potent stimuli for secretion, and may cause water retention even in the presence of hypoosmolality, whereas hypervolaemia blunts the release of AVP in response to increase in osmolality (24).

OT is synthetised in the hypothalamus, in nerve cells close to those who synthetise AVP, and also transported to the posterior hypophysis where it is released. Lactation appears to be the only function depending exclusively on OT (25). OT stimulates myometrial contraction and is commonly administered for induction and augmentation of labour, but is not essential for labour and delivery (26). OT may also cause water retention by stimulation of the V2 vasopressin receptors in the kidney. The infusion rate of OT must exceed 20 mU/min to cause antidiuresis in humans (27) which will be reached at the infusion rate of 20 milliliter per hour of OT 5 IU in 500 milliliter. However, the antidiuretic effect will cease when infusion is stopped.

The AVP receptors, V1, V2, V3, and the OT-receptor belong to the G protein-coupled receptors and are structurally very similar explaining the pronounced cross reactivity of the two hormones (20). Noteworthy, whereas AVP and OT have similar affinity for the OT receptor, the affinity for V2 receptor by OT is 30-fold lower compared to AVP (28). The AVP receptors are not down regulated during prolonged stimulation, whereas the OT receptor effectively is down regulated during prolonged stimulation during labour (26). Studies have also shown that the myometrium is more sensitive to AVP than to OT (26).

V1 receptors (formerly V1a) are found in the central nervous system, vascular smooth muscle cells, liver, and platelets. The foremost effect is vasoconstriction, and 90 % of circulating AVP is bound to platelets. V2 receptors are found in the collecting ducts of the kidney, and stimulation leads to increased water reabsorption through incorporation of aquaporine 2 (22). V3 receptors (formerly V1b) are found in the adenohypophysis, and corticotropin is released following stimulation.

1.2.1 Copeptin

AVP is produced as a larger precursor called preprovasopressin in the paraventricular and in the supraoptic nucleus of the hypothalamus (29). During axonal transportation to the neurohypophysis the provasopressin is separated from the signal peptide, thereafter AVP is separated from neurophysin and the C-terminal peptide, also called copeptin. OT lacks the C-terminal peptide, all copeptin therefore originates from the provasopressin.

The study of AVP is difficult as half life is short, and the analysis is hampered with methodological difficulties and high costs. Copeptin was first described in 1972 (30), but a reliable immunoluminometric assay for analysis of copeptin was developed first by Morgenthaler in 2006 (31). The identification of copeptin, its release in a 1:1 manner with AVP, together with commercially available methods for analysis have therefore brought new insight into the physiological properties and importance of AVP. The analysis requires only 50 µl of blood, and the cost although still high, is currently decreasing. Analysis of copeptin may therefore become important also in everyday clinical practice (32).

Copeptin levels in physiological and pathological conditions were first described in adults (33). From 5 pmol/L at rest, copeptin levels increased with dehydration and moderate stress, reaching the highest level during septic shock when a 20-fold increase in copeptin was described (30,33). Birth has been recognised as an extremely stressful experience for the fetus with a surge in stress hormones (34). Wellman found that copeptin in newborn immediately after vaginal delivery exceeded by 5-10 times the highest levels previously described in adults

(35). The highest levels in newborn were found following prolonged labour and instrumental vaginal delivery, and copeptin levels were inversely correlated to umbilical arterial pH at birth. In contrast, values close to resting levels were found in infants delivered by planned caesarean section. Copeptin was also higher in arterial compared to venous umbilical blood, indicating fetal origin of copeptin, confirming previous research that indicated independent fetal osmoregulation (36).

1.2.2 Respiratory effects of osmolality

Osmolality and strong ions have been proposed as important contributors to chemical respiratory control (37,38). Several studies show that changes in osmolality may influence ventilation. Increased osmolality inhibited panting in dogs (39) and opposed sweating and ventilatory response to hyperthermia in humans (40,41). This is interpreted as suppression of water dependent thermoregulation in dehydrated mammals, as the preservation of body fluid is preferred even at the cost of increased core temperature (42). On the other hand, animal studies also indicated that decreased osmolality stimulates ventilation (5). Most human studies in this field have employed a spontaneously occurring human model, as decrease in osmolality and SID are observed in pregnancy and these changes are present to a lesser degree also in the luteal phase of menstruation (43). These studies showed that $PaCO_2$ was predicted by changes in osmolality and SID (4,38) and also correlated progesterone to $PaCO_2$. However, relaxin, secreted by the corpus luteum already during the luteal phase of the menstrual cycle, has replaced progesterone as the hormone considered responsible for lowering of plasma sodium in early pregnancy (44).

Release of AVP is controlled by central osmoreceptors situated in areas in the hypothalamic region that are at least partly located outside the blood-brain barrier (23). Therefore, the numerous angiotensin receptors present in the Organum Vasculosum of the Lamina Terminalis are accessible to circulating ANG II (23). Electric stimulation in the Subfornical Organ has been described to stimulate respiration in rats (45). These facts may explain the less well known respiratory effects of ANG II. Anderson found that reduction in osmolality stimulated breathing in dogs, and that decrease in $PaCO_2$ was correlated to plasma renin activity and osmolality (5). Other animal studies corroborate involvement of ANG II in respiratory regulation as intravenous infusion of ANG II stimulated ventilation, and angiotensin receptor blockers blunted the ventilatory response to hypotension (23,46,47). ANG II also stimulates thirst and AVP release, and AVP in turn antagonises the ventilatory stimulation by ANG II and exerts some inhibitory feedback on renin release (23,48). ANG II and AVP thus integrate regulatory

systems of volume and osmolality, and changes in osmolality are integrated with other vital functions, such as breathing and vasomotor control (49).

1.2.3 Osmolality and plasma sodium in pregnancy

Osmolality is maintained at a close range of 285-290 mOsm in the non-pregnant human, but in the pregnant woman osmolality is reduced by approximately 10 mOsm (11). Reduction in plasma osmolality is mainly a result of a decrease in plasma sodium by 3-5 mmol/L. By 12 weeks of gestation this adaptation has stabilised, and plasma osmolality remains low until after delivery (11).

Threshold for thirst and release of AVP is lowered, but release of AVP in response to adequate physiological stimuli correspond to the non-pregnant state. A lower osmolality is maintained indicating a "reset "of the osmostatic control (11). The hyponatraemia of pregnancy is therefore not a result of inappropriate ADH secretion as might be seen in the homonymous syndrome. Animal studies show that osmosensitive neurons in the hypothalamus, directly or indirectly, respond in similar manner to hypertonicity, ANG II, and relaxin (18).

1.2.4 Vasopressin in pregnancy

Basal levels of AVP are unaltered during pregnancy, but the metabolic clearing rate of AVP increases from early pregnancy due to an increase in circulating AVPase produced by the placental trophoblasts. The level of AVPase increases fourfold reaching its maximum by term, and the enzyme is inactivated in the liver (50,51). Central diabetes insipidus (DI) may occur when AVP degradation rate exceeds rate of synthesis. Manifest DI is a rare complication to pregnancy, complicating 1: 30 000 pregnancies (52). DI is usually described in women with multiple pregnancies with higher trophoblast production of AVPase, or in women with impaired hepatic AVPase degradation due to preeclampsia, liver steatosis or the syndrome of hemolysis, elevated liver enzymes, low platelets (HELLP) (52). However, some authors have proposed that subclinical DI could be more common during late pregnancy than commonly assumed (50,53).

DI may be treated with the synthetic AVP analogue desmopressin that only stimulates the V2 receptors. AVPase will not inactivate desmopressin as this synthetic analogue differs from AVP with a modified N-terminus and an alteration to arginine in position 8 (54). Therapeutic indications for desmopressin are enuresis and central DI. In 10-20 times higher dosage desmopressin has haemostatic effects increasing plasmatic levels of factor VIII and von Willebrand factor as well as increasing platelet adhesiveness (55). Desmopressin is therefore

administered both in patients with known bleeding disorders and when platelet dysfunction is suspected as might occur following large obstetric bleeding. Half life of desmopressin is 6-10 hours, by far exceeding that of AVP, hence the antidiuretic effect is long-lasting, up to 24 hours. A meta analysis indicated that women are more sensitive to the antidiuretic effects of desmopressin than men (56). These characteristics of desmopressin could have relevance when the drug is administered to the obstetric patient.

1.2.5 Feto-maternal electrolyte and albumin relationship

Neonatal plasma sodium at birth varies greatly, as normal values vary between 133 and 144 mmol/L (57). In literature fetal plasma sodium is reported equal or lower than maternal plasma sodium (58,59). One study found that fetal chloride was higher than maternal chloride at all stages of pregnancy (60). Fetal albumin is reported to be higher than maternal albumin at term (61-63).

1.3 HYPONATRAEMIA

Plasma sodium levels vary between 136-146 mmol/L in non-pregnant subjects, but during pregnancy sodium decreases and normal range is 127-140 mmol/L (64). Hyponatraemia is usually defined as a decrease in plasma sodium level below 136 mmol/L (19), but this definition is obviously not applicable to pregnant women. More important than the absolute level of hyponatraemia is the speed with which it has developed (19). Hyponatraemia is defined as chronic when it has lasted longer than 48 hours, acute when it has developed within 24 hours (65). Plasma sodium of 128 mmol/L was the highest level of plasma sodium that caused severe neurological symptoms in acute hyponatraemia (66), compared to levels as low as 110 mmol/L not rarely seen in the almost asymptomatic patients with chronic hyponatraemia, often due to treatment with tiazide diuretics (65).

Hyponatraemia causes increase in interstitial and intracellular fluid volume. Pulmonary oedema may develop, and cellular swelling principally causes neurological symptoms. Initial symptoms of cerebral oedema are irritability, headache, nausea and vomiting, and subsequently, convulsions and coma can occur. Severe hyponatraemic encephalopathy can cause respiratory arrest and death (66).

1.3.1 Female sex hormones and sensitivity to hyponatraemia

The highest morbidity and mortality in hyponatraemic encephalopathy is seen in women of fertile age (24). This is believed to be caused by oestrogen that reduces the Na^+-K^+ ATPase pump activity in the brain. As a consequence sodium is hampered from leaving the brain

astrocytes which will impede intracellular equilibration with lower extracellular osmolality. This will cause cell swelling that may lead to severe neurological symptoms. Seizures, respiratory arrest, and brain stem herniation causing death are more frequently seen when women develop hyponatraemic encephalopathy (24,67).

1.3.2 **Chronic hyponatraemia**

Chronic hyponatraemia is by definition hyponatraemia that has lasted longer than 48 hours (65). The lowering of plasma sodium may be due to excess body water, or more rarely to a lowering of total body sodium. In the syndrome of inappropriate ADH secretion (SIAD) dilutional hyponatraemia is caused by retention of water due to secretion of AVP in absence of physiological osmotic or non-osmotic stimulation (68). However, some authors consider only osmotic stimulation to be appropriate thereby creating confusion regarding the definition of SIAD (65). SIAD may be seen in thyroid, neurological or pulmonary diseases, and may also be pharmacologically induced. Chronic hyponatraemia needs to be corrected slowly, with a maximum rise of 24 mmol/L sodium in 48 hours, as the rise in plasma sodium should not exceed 0,5 mmol/L per hour. A faster correction may result in periventricular leucomalacy, a condition that may lead to severe neurological impairment. Aggressive correction with hypertonic saline is indicated only in the presence of severe neurological symptoms, which is rare in cases of chronic hyponatraemia. Water restriction and causal therapy are usually the only necessary treatments. The actual value of plasma sodium should not guide the intervention.

1.3.3 **Acute hyponatraemia**

A lowering of plasma sodium below 136 mmol/L, or 130 mmol/L in the pregnant woman, and that has developed within 24 hours is considered acute (65). The speed of lowering of plasma sodium is more important than the actual level of plasma sodium. Ingestion or administration of an excess water load may cause acute hyponatraemia, and subjects with high level of AVP are at particularly high risk. Pain, stress, and fear are non-osmotic stimuli for AVP secretion, but hypovolemia and hypotension are the most potent stimuli for AVP secretion and may cause water retention even if osmolality is low (24). Patients are therefore particularly vulnerable in the perioperative setting, when a multitude of non-osmotic stimuli are present.

Several cases of serious and even lethal hyponatraemia have been described postoperatively and the highest morbidity and mortality rates in hyponatraemic encephalopathy are found in women of fertile age (24,67). Lethal hyponatraemia has also occurred when large volumes of free water were ingested (69). Several healthy individuals have died from hyponatraemia

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during endurance sports, and researches argued for decades about the pathophysiology in the condition known as endurance associated hyponatraemia. Individual characteristics such as gender or other genetic predisposing conditions and SIAD were discussed. However, a large prospective observational study conducted during the Boston marathon in 2002 showed that hyponatraemia was caused by excess water (70). Longer running time, together with very high or very low BMI, was also related to the development of hyponatraemia, explaining why female gender was previously considered a possible risk factor for hyponatraemia.

1.3.4 Hyponatraemia during labour

The threshold for thirst and release of AVP is lowered during pregnancy, but release of AVP in response to adequate physiological stimuli correspond to the non-pregnant state. A lower osmolality is maintained indicating a "reset "of the osmostatic control (11). Retention of water and sodium causes dilutional hyponatraemia and is not a result of inappropriate ADH secretion (SIAD). Acute hyponatraemia in addition to this chronic hyponatraemia may develop during labour, and severe and fatal cases were described already in the 1960ies (8,9).

In an observational study published in 1981 Tarnow-Mordi found that hyponatraemia was iatrogenic, mainly caused by hypotonic fluids administered intravenously (8). Hyponatraemia correlated to administration of OT and to epidural analgesia. For safety reasons OT was administered in dilute solutions, and labour epidural analgesia was at the time provided exclusively by local anaesthetics in concentrations of 1.25-5 mg per milliliter, which could cause hypotension. Intravenous cristalloids were therefore administered as preventive measure. The development of pump devices have permitted more concentrated solutions of OT, and with the addition of opioids lower concentrations of local anaesthetics are required for epidural analgesia.

These changes have reduced the need for intravenous cristalloids, however, also in recent years several case reports of hyponatraemia during labour have been published (6,7). In most cases maternal or neonatal seizures have led to the diagnosis of severe hyponatraemia. Studies in sports medicine claiming that hydration was essential for optimal muscle performance inspired obstetricians to hypothesise that hydration could reduce duration of labour (71,72). However, a subsequent Cochrane report could not support the liberal administration of intravenous fluids during labour (73).

Guidelines encouraging women to drink at least 500 milliliter per hour during labour and to drink to avoid thirst are still to be found on Swedish websites (74), but in a more recent publication the responsible midwife has reduced the advised hourly fluid intake to one small

glass of water (75). Diagnostic difficulties of hyponatraemia during labour are obvious, as initial symptoms of hyponatraemic encephalopathy are nonspecific and may easily be confused with symptoms of preeclampsia.

1.3.5 Health by drinking water, where is the scientific evidence?

Researchers in sports medicine proposed for more than 30 years new principles for optimal muscle performance stating that loss of body weight was directly correlated to decreased muscular performance in endurance sports (69). The concept of "voluntary dehydration", well known in the elderly, was extended also to young and fit athletes, and to prevent dehydration the principle of drinking so much as to avoid the sensation of thirst was advocated. These principles were almost universally accepted, and among the public there still is a widespread belief that drinking large quantities of water promotes health. In a thorough review of the literature Valtin could not find evidence for this assumption, nor did he find its origin (76).

 The practice of ingesting large quantities of fluids during endurance sports has led to several fatalities due to hyponatraemia. A long lasting conflict raged between supporters of ingestion of fluids to prevent weight loss and those advocating thirst as the guide to fluid ingestion (77). It is now accepted that excessive fluid intake causes exercise associated hyponatraemia, however, hyponatraemia still occurs among athletes (78,79). A recent internet search for guidelines regarding fluid intake during endurance sports revealed that overdrinking was still advocated (80).

Midwives often argue that labour is extremely energy consuming, and several studies have addressed the various nutritional policies and their effect on labour (81). One large prospective randomised trial showed that light meals compared to water only was neither beneficial nor harmful for the mother´s wellbeing or the process of labour (82). Following publication of these studies professionals as well as the public have questioned the "nil per mouth" policies common in labour wards in many parts of the world. In Sweden women have usually been allowed fluids and in some labour wards even solids, therefore these studies have not caused significant change in policies regarding food and drink during labour in Sweden.

1.4 STEWART´S PHYSICO-CHEMICAL APPROACH TO ACID–BASE BALANCE

Stewart proposed in 1983 a physico-chemical approach for analysis of the correlation between electrolytes and acid-base balance (83). New definitions of the metabolic components in the acid –base analysis are cornerstones in this model. These are the strong ion

difference (SID), determined by the difference between the strong cations and anions, the non-volatile weak acid buffer (A-tot), mainly determined by the albumin concentration (84), and, of lesser importance, the unmeasured anions (UA) made up by sulphates, phosphates, and other anions that may be present in pathological conditions. SID, A-tot, and UA are the independent variables in Stewart´s model that determine the dependent variables pH and HCO_3^-. Particularly the definition of HCO_3^- as dependent variable challenges the conventional model of acid-base analysis that may even advocate infusion of HCO_3^- for correction of metabolic acidosis. SID is usually about 40 mEq/L, and the "gap" is filled up with the components of the buffer base, consisting of the weak anions HCO_3^- and A-tot (85). A decrease in SID is associated with a decrease in buffer base causing metabolic acidosis, and an increase in SID and buffer base will result in metabolic alkalosis. Decrease in A-tot, as seen in hypoalbuminaemia or haemodilution, will likewise cause metabolic alkalosis. Any effect on acid-base balance will be the result of changes in SID, A-tot, and if present, changes in UA.

The SID in this simplified description of Stewart´s model is more correctly described as SID apparent (SIDa). However, as the independent variables influence each other, the more exact calculations require factorial correction. The SID corrected is referred to as SID effective (SIDe) (91). However, this distinction is not made in this thesis.

The value and clinical relevance of Stewart´s model have been questioned, and in everyday practice the original formulas and calculations might have caused more confusion than understanding. However, nowadays APPs are available to assist clinicians, facilitating previously difficult calculations (86).

Stewart´s principles have also created a general appreciation of the relationship between electrolytes and acid-base alterations. Metabolic acidosis caused by infusion of "normal saline" 0,9 % was first described by Scheingraber and is now widely recognised (87). One study clarified the effects of acetazolamide, used for correction of the additional and primary metabolic alkalosis that often occurs in patients with $PaCO_2$ retention due to chronic pulmonary disease (88). This study showed that acetazolamide increased plasma chloride and thereby reduced the metabolic alkalosis. The reduced urinary excretion of chloride and the increase in urinary bicarbonate caused alkalinisation of urine. This study supports Stewart´s description of acid-base effects of electrolytes. Gattinoni showed that electrolytes have acid base effects of only if plasma is equilibrated with CO_2 (89).

1.4.1 Interpretation according to Stewart of pregnancy induced changes

The lowering of plasma sodium typical of early pregnancy will cause a decrease in SID and metabolic acidosis. A physiological decrease of albumin will partially compensate the acidosis, as albumin is a weak acid. The respiratory compensation for the resulting metabolic acidosis will decrease $PaCO_2$. Thus, according to this analysis, the metabolic acidosis is primary and the respiratory alkalosis is compensatory. Stewarts approach has also been adopted for greater understanding of preeclampsia. One study performed acid-base analysis by the Stewart-Gilfix approach in healthy pregnant women and women with preeclampsia (90). A conventional analysis would not have revealed any dissimilarities as base excess was similar in both groups, but the difference in metabolic components became apparent when adopting the Stewart-Gilfix approach. The lower albumin in preeclamptic women compensated for a probable increase in UA, and the authors suggested that albumin levels could be a prognostic factor for the severity of the condition.

1.5 MYOMETRIAL CONTRACTILITY

Coordinated and forceful myometrial contractions are necessary for labour and delivery, and quiescence during pregnancy until term is a prerequisite of normal pregnancy. The physiology of myometrial contractility is extensively studied but still not completely understood. Contractions are ultimately determined by influx of calcium, and several ions and different ion channels contribute to the complex processes, and sodium is involved in several of these (91,92). Animal studies have showed reduced contractility in myometrial biopsies immerged in fluids with low concentration of sodium (93). A slow sodium leak channel has been identified and is believed to reduce the membrane polarisation facilitating the action potential (AP) that causes contractions (94). A fast sodium channel, particular to the myometrium and absent in other smooth muscle cells, has been identified in rat uterus, increasing significantly in number towards term (95). This fast sodium channel could be involved in the propagation of impulses and also enhance influx of calcium. Calcium is exchanged with sodium ending contractions (96), and Na^+-K^+ pumps are also involved (91). Thus, there are several possible ways alterations of extracellular sodium concentrations may affect myometrial contractility.

The role of calcium is particular to the uterus, as the influx of calcium both generates APs and the following contraction (96). Influx of ions is believed to reduce the membrane polarisation to a level when the low-voltage fast T-type calcium channel opens causing depolarisation, and contraction occurs mainly due to inflow of extracellular calcium through the activation of high-voltage L-type calcium channel (96).

The APs may be one of two types, spike- type or plateau- type (96,97). The spike-type APs are shorter lasting, and therefore permit lesser influx of calcium, resulting in ragged multi-component contractions with relatively higher frequency (97). The plateau-type APs are more longer lasting and therefore permit larger influx of calcium through the L-type calcium channels generating more forceful contractions with a smooth appearance (98).

Recent studies have described the curves of isometric contraction by analysing the traces of force and its first derivate. The resulting phase portrait plots indicate that contractions following the spike-type APs would be less effective compared to the contractions that follow plateau-type APs (96,99).

Studies also have shown that strips from the same biopsy may present both spike-like and plateau-like APs (96), and also that only fibres, but not isolated muscle, cells can exhibit long-lasting APs indicating the importance of cellular network (96,99). OT enhances calcium influx and may transform spike-type APs into plateau-type APs and increase the duration of the plateau, which results in more forceful contractions (100). Hyperpolarisation follows the plateau-type AP but is not seen after the spike-type AP, and importantly, APs are not observed during hyperpolarisation (98).

Some studies have shown higher delivery rates and also increased premature deliveries in the days following religious fast, the so called Yom Kippur effect (26,101). There is no obvious explanation for this, but increased osmolality due to fasting would be a physiologic stimulation for AVP, therefore the impact of this hormone on myometrial contractility cannot be excluded. Studies have also shown that the myometrium is more sensitive to AVP than to OT (26).

AIMS

This thesis was designed to study causes and effects of changes in plasma sodium and osmolality during pregnancy and labour.

Study 1

To investigate the impact of osmolality on ventilation, with the hypothesis that increased osmolality would decrease ventilation independently of gender, and that a decrease in osmolality would stimulate ventilation not only in women but also in men.

Study 2

To investigate the occurrence of hyponatraemia following labour and delivery, with the hypothesis that hyponatraemia may be more common in labouring women than assumed.

Study 3

To determine a possible influence of hyponatraemia on myometrial contractility, with the hypothesis that hyponatraemia negatively affects contractility.

Study 4

To investigate feto-maternal osmotic relationship at term with the hypothesis that, in contrast to literature, maternal plasma osmolality is lower than fetal levels.

MATERIAL AND METHODS

This section includes main features of the material and methods used in the studies. Detailed description can be found in the separate papers.

Ethical considerations

Studies1, 2, and 4 were approved by the Regional Ethical Board at the University of Linköping, Sweden. Study 4 was approved by the Regional Ethical Review Board in Stockholm, Sweden. All patients and volunteers signed written informed consent before inclusion.

Paper 1 Osmolality and breathing

Our study participants were healthy volunteers of both sex. Ten men (mean 28 years; range 20-40) and nine women (mean 33 years; range 22-43) were included. All women participated both in the follicular and luteal phase of the menstrual cycle. Each woman participated on four separate occasions, whereas the men participated twice.

The subjects fasted from midnight, and had a light breakfast at home, arriving in the laboratory at 0800 in the morning. Following infiltration anaesthesia, a 20 G arterial line was placed in the radial artery and, when required, an 18 G venous line was placed. Hyperosmolality was induced by intravenous infusion of hypertonic saline 3%, and hypoosmolality by drinking tap water. Heart rate, invasive arterial blood pressure, and pulse oximetry were continuously measured during the whole observation period. Sensitivity to CO_2 was determined by rebreathing tests performed before and after the fluid loading procedures. Arterial blood samples were collected after 30 minutes of rest (baseline), before and after the rebreathing tests, and every 20 minutes during the fluid loading procedures, as well as 1 hour after study termination. Blood gases, sodium, chloride, glucose, and haemoglobin were analysed in all blood samples by a point-of-care analyser. At baseline and after the fluid loading procedures blood samples were sent to the central laboratory for analysis of albumin, urea, and osmolality determined by cryoscopy. For further details see study 1.

Fluid loading procedures

Water loading; the participants drank tap water 20 ml· (kg body wt)$^{-1}$·h^{-1} for 2 hours. This was administered as an initial volume of 400 ml of water, followed by 150-200 ml every 10 minutes for 2 hours, up to a total of approximately 2.5 liters.

Hypertonic saline: Saline 3% was infused intravenously at the rate of 0.1 ml·(kg body wt)$^{-1}$·min^{-1} for 120 minutes, up to a total of approximately 1 litre.

Rebreathing test

The subjects were placed in a semirecumbent position, with the head supported by a pillow. A nose-clip was applied, and after breathing room air for 30 seconds through a mouthpiece with a heat-moisture exchanger and a capnograph, a modified Bain system without CO_2 absorber was attached. The modified Bain system consisted of a 900 cm long, 30 mm wide tube with an open end (102). The internal volume of the tube was 6.4 litres, and close to the mouthpiece was a tube for fresh gas inflow of air with 30% O_2, calculated as 75 ml (kg body wt)$^{-1}$· min^{-1}. The rebreathing test continued for 10 minutes, when steady state was assumed to be reached. Close observation of the capnograph traces ensured that no breathing of CO_2 free room air occurred. Respiratory rates, inspired fraction of O_2 and end tidal (ET) CO_2 were recorded. Arterial blood samples were collected immediately before the rebreathing test, and at steady state. ET CO_2 was correlated to $PaCO_2$.

Statistics

Power calculation

Drinking water 20 ml·(kg body wt)$^{-1}$·h^{-1} for 2 hours can decrease plasma osmolality by 5 mOsm/kg (43,103). Intravenous infusion of hypertonic saline 3% at the rate of 0.1 ml·h (kg body wt)$^{-1}$· min^{-1} for 120 minutes can be expected to increase plasma osmolality by at least 10 mOsm/kg (43,104). Plasma osmolality is predictably altered in both cases, and the effect on $PaCO_2$, if any, should be present. With 10 paired comparisons, and a 3 % coefficient of variation of plasma osmolality, plasma sodium, and $PaCO_2$, 10 persons in each group would be sufficient to detect 5 % changes of $PaCO_2$ with power of > 90%.

Analysis of results

Variables sampled during the loading procedures were analysed using repeated measures ANOVA with the various subject groups as categorical predictors either using all sampling occasions, sampling occasions at the end of the rebreathing tests, or sampling occasions during the loading procedures. Decreased SID indicates metabolic acidosis according to the Stewart model. We therefore assessed base excess (BE), pH, and $PaCO_2$ at the time where SID reached its lowest level in each individual during the fluid loading procedures, and differences from baseline was calculated for these variables. In order to investigate interrelationships between $PaCO_2$ and SID, linear regressions were made individually for each subject. In both cases, ANOVA was used to assess differences from baseline with groups as categorical predictor for group differences.

Reliability

In our statistics we used the calculated values of plasma osmolality, obtained at all sample occasions. A Bland-Altman plot was created to compare these calculated values of plasma osmolality with serum osmolality determined by the method of cryoscopy, measured at baseline and immediately after termination of the fluid loading procedures. The Bland-Altman plot showed that the calculated values for plasma osmolality were consistently 12 units lower (4%) compared to the measured values for serum osmolality, but showed no coupling to osmolality levels. Changes are therefore independent of method.

The methodological intraindividual error of the rebreathing test was calculated using the S-method first proposed by Dahlberg (105):

$$S_{method} = \sqrt{(\sum d_i^2 / 2n)}$$

where d_i is the difference between the i:th paired measurement and n is the number of differences. The methodological intra individual error of our rebreathing test was 10% for all groups.

Formulas for calculation

Plasma osmolality mOsm/kg = 2[Na] + [glucose]

SID mmol/L= ([Na]+[K]) - [Cl]   (85):

Paper 2 Hyponatraemia during labour

Pregnant women were informed about the study during antenatal classes. All women at term (37 full gestational weeks) were eligible with patient refusal as the only exclusion criterion. 308 women were included in the study. Complete data from 287 women (125 primiparas and 162 multiparas) were included for calculation of results.

Hyponatraemia could not be expected to develop during shorter lasting labours, and therefore women were recruited to permit the inclusion of at least 30 women in each of four groups composed according to duration of labour and obstetric outcome. In addition 30 women delivered by planned caesarean section were included as controls. The study continued until completion of all five groups. Postnatal data from infants affected by significant congenital malformation or disease, meconium aspiration, or sepsis were excluded from analysis.

Oxytocin for augmentation of labour was administered in 5 % glucose at a concentration of 20 mU/ml. Intravenous glucose could also be ordered by the obstetrician as caloric supplement. Ringer's acetate was administered intravenously during epidural analgesia. Ringer's acetate and ephedrine were administered intravenously for blood pressure control during caesarean section under regional anaesthesia. General anaesthesia was performed only in cases of emergency. The volume of Ringer's acetate administered before delivery by caesarean section was estimated to 600 milliliter in all patients. The women were allowed to drink freely during labour, but no solids were permitted.

All oral intake was registered, and combined hourly fluid consumption was calculated after delivery. Information regarding duration of labour, pain relief, and delivery was recorded as well as Apgar and any pathology in the infants´ first days of life.

Blood samples were collected from the mothers on admission and as soon as possible following delivery. Clamped cord blood samples from umbilical artery and vein were collected. All blood samples were analysed for haemoglobin, sodium, glucose, and blood gases with a point of care analyser. Plasma osmolality in maternal blood samples was analysed by the method of cryoscopy.

Statistics

Power calculation

Patients were recruited to permit the inclusion of at least 30 women in each of four groups composed according to duration of labour and obstetric outcome. In addition 30 women delivered by planned caesarean section were included as controls. A mean decrease of the sodium concentration of 5 mmol/L during labour would be considered significant. The sample size of at least 30 women in each group was required for a 90 % power to detect a significant difference with a two-sided alpha error of 0.05.

Analysis of results

For analysis the women were reallocated to three new groups according to total fluid administration during labour. Women with missing data were excluded from analysis. Continuous variables were compared with Kruskal Wallis non-parametric test and categorical variables with Chi-square test if the number of subjects was appropriate, otherwise Fisher´s exact test was used. Univariate and multivariate logistic regression were performed to study the relationship between maternal hyponatraemia and parity, age, body mass index (BMI), as well as fluid volumes administered, epidural analgesia, and oxytocin during labour. All tests were two-tailed, and a p-value of < 0.05 was considered statistically significant.

Paper 3 Hyponatraemia and myometrial contractility

We obtained myometrial biopsies from 17 women (age 29-42, median 35) during planned caesarean section in spinal anaesthesia at term. Each biopsy was divided into 8 strips and mounted isometrically in a force transducer. Seven biopsies were used in the first part of the study. Half of the strips were immersed in the hyponatraemic study solution S containing Na 120 mmol/L and observed for 60 minutes, followed by 60 minutes in the normonatraemic solution C containing Na 136 mmol/L, then again immersed in solution S for 60 minutes, and finally for 60 minutes in solution C. The other half of the specimens were studied in reverse order, being immersed for four periods of each 60 minutes in the solutions C-S-C-S. In the second part of the study ten biopsies were included to study the response to increasing doses of oxytocin in solution S and C.

Solutions

Tyrode´s solution with Na 136 mmol/L used for transport and control contained (in mmol/L) NaCl 114, KCl 4,0. $CaCl_2$ 2,0, $MgCl_2$ 1,0, $NaHCO_3$ 21,4, NaH_2PO_4 1,4, Glucose 10

Hyponatraemic study solution: Tyrode´s solution with Na 120 mmol/L contained (in mmol/L) NaCl 97,4, KCl 4,0. $CaCl_2$ 2,0, $MgCl_2$ 1,0, $NaHCO_3$ 21,4, NaH_2PO_4 1,4, Glucose 10. The solutions were equilibrated with a gas mixture of 95% O_2 and 5% CO_2.

Phase portrait plots

The curves of isometric force are used to create phase portrait plots by plotting the first derivate of the force versus isometric force (7).

Statistics

Analysis of results

Differences in frequency, amplitude, and area under the curve (AUC) in solution S and solution C were analysed with Wilcoxon matched pairs test. Initial multiphasic contraction rates with increasing doses of oxytocin in solutions S and C were analysed with ANOVA. All tests were two-tailed, and a p-value ≤0. 05 was considered significant.

Paper 4 Feto-maternal osmotic relationship

We included in the study 42 healthy women with singleton pregnancy scheduled for elective caesarean section in spinal anaesthesia at term (38-39 weeks). However, complete data were obtained from only 30 women, and only the results from these women were included for analysis. Maternal exclusion criteria were preeclampsia, diabetes mellitus, BMI above 40 kg/m2, renal disease, active inflammatory bowel disease, or any other condition that could infer with water and electrolyte balance. Only pregnancies with healthy fetuses and newborn were included.

The women fasted from midnight, but were allowed clear fluids until two hours before the caesarean section, scheduled to be performed in the morning. Upon arrival in the operating theatre an intravenous cannula was placed in the antecubital vein, and blood samples were collected before beginning intravenous administration of acetated Ringer´s solution which started simultaneously with the administration of the anaesthetic (co-hydration). Spinal

anaesthesia was performed in the sitting position with hyperbaric bupivacaine 11-12.5 mg, fentanyl 12.5 µg, and morphine 0.1 mg, and the mothers were immediately placed in the supine position with left lateral tilt. Blood pressure was maintained with intravenous bolus doses of phenylephrine 25-50 µg, oxygen was delivered by nasal cannula at 2 litrer per minute. Monitoring included electrocardiography, non-invasive blood-pressure recorded every 2 minutes, and pulse oximetry. Delayed cord clamping for 2 minutes was adopted as by routine and Apgar scores were recorded at 1, 5 and 10 minutes.

Locations, sampling procedures, and methods for analysis

We sampled blood from mothers immediately before caesarean section and from the umbilical artery and vein before cord clamping. All maternal and fetal blood samples were collected in 2 mL syringes pre-heparinised with 30 IU of balanced heparin. Within 5 minutes the point-of care analyser ABL 825 Flex analysed whole blood for blood gases, plasma sodium and chloride with potentiometry using direct ion selective electrode (ISE). The remaining blood was transferred from the 2 mL syringes into two microcontainers and immediately sent to the central hospital laboratory for comparative analysis. The microcontainers used for analysis of electrolytes and albumin were pre-heparinised with 0.1 mg of lithium-heparin, the microcontainers used for analysis of osmolality were free of additives. The microcontainers were centrifuged in the central laboratory as soon as possible after arrival and the supernatant plasma was analysed for sodium by the method of potentiometry, also using direct ISE. Plasma osmolality was also immediately analysed by the method of cryoscopy. The syringes and microcontainers were gently rolled 10 times after filling, and a minimum of 1.2 milliliter blood was required for the performance of all analysis.

Statistics

Power analysis

Based on the results from study 2 mean sodium difference of 2 mmol/L between mother and arterial cord was considered clinically significant. The sample size of 32 women and their newborn was required to achieve 90% power to detect a significant difference with a two sided alpha error of 0.05 with a SD of 2.5 mmol/L.

Analysis of results

Residuals of osmolality, sodium, and albumin were normally distributed. For graphic presentations paired differences were analysed using main effects ANOVA with method or patient identity as categorical predictors. Sodium was adjusted for albumin using analysis of

covariance (ANCOVA) and shown in the same graph. Differences between groups were also analysed with paired t-test and presented in tables. All tests were two-tailed, and a p-value of less than 0.05 was considered significant.

RESULTS

All results are presented and statistically evaluated in the separate papers. This section features the most important results.

Paper 1 Osmolality and breathing

Twenty-five subjects were included in the study, but complete results were obtained only from the 19 who fulfilled the investigation, ten men (mean 28 years; range 20-40) and nine women (mean 33 years; range 22-43) .Three groups were analysed: 1) men, 2) women in the follicular phase of menstruation, and 3) women in the luteal phase of menstruation. There were no differences in BMI between men and women, but men had significantly higher systemic blood pressure (p=0.005). Women in the luteal phase had significantly lower $PaCO_2$ and SID compared to men (p=0.002, p=0.01, respectively.) For women in follicular phase, the differences were not significant, (p=0.1, p=0.5, respectively). All changes were similar in men and women, with no difference between the follicular and the luteal phase. We therefore show the pooled results for all three groups in figure 1.

For further details see study 1.

Water loading

The women drank on average (SD; range) 2758 (254; 2444-3160) milliliter water, the men drank 3170 (245; 2640-3480) milliliter water. Water loading caused reduction in plasma sodium, chloride, osmolality, as well as SID and BE in all individuals (Fig 1). A decrease in $PaCO_2$ was observed (p=0.005, Fig 1D), and pH remained unchanged (Fig 1C).

Salt loading

The women received on average (SD; range) 828 (76; 733-948) milliliter saline 3%, the men received 951 (74; 792-1044) milliliter saline 3%. Salt loading increased plasma sodium and osmolality in all individuals (Fig 1). Analysis of pooled data showed absence of respiratory compensation (Fig 1 D). SID and BE were reduced, but arterial $PaCO_2$ remained constant (Fig 1D), and pH decreased (p<0.001, Fig 1C).

Sensitivity to CO_2

We found no difference in $PaCO_2$ increase during the rebreathing tests before or after the fluid loading procedures (p=0.48, Fig 1 D).

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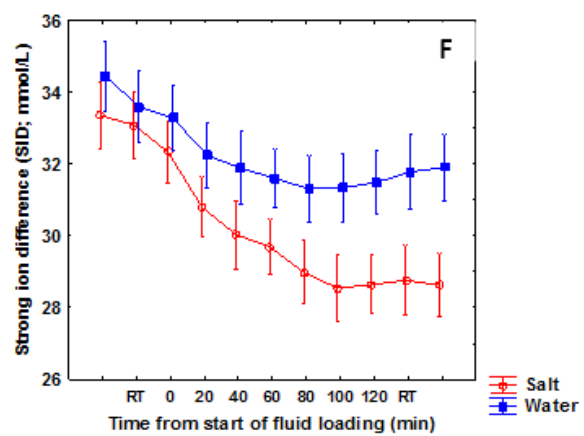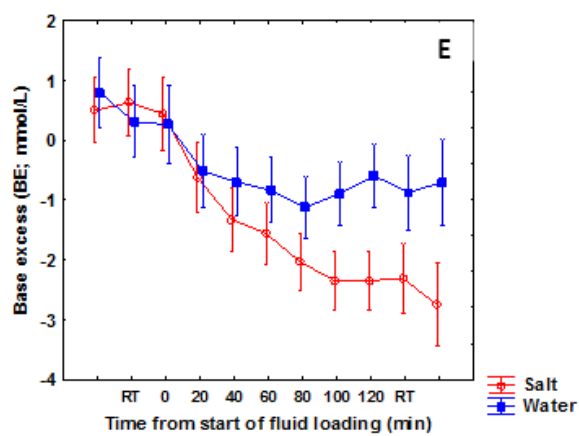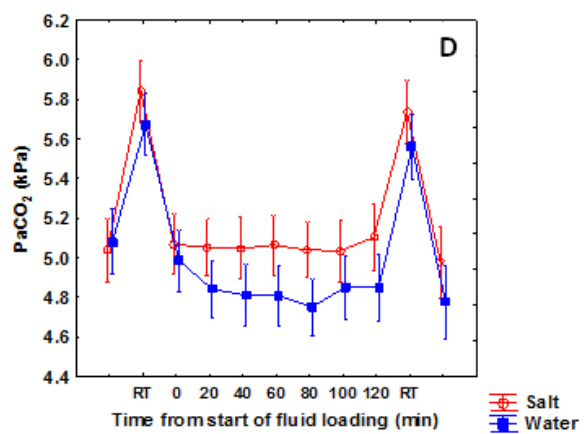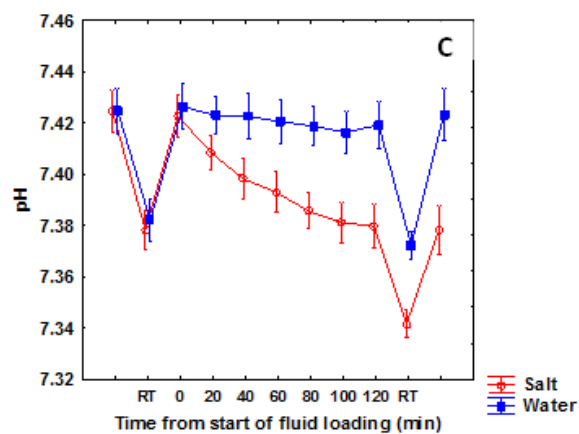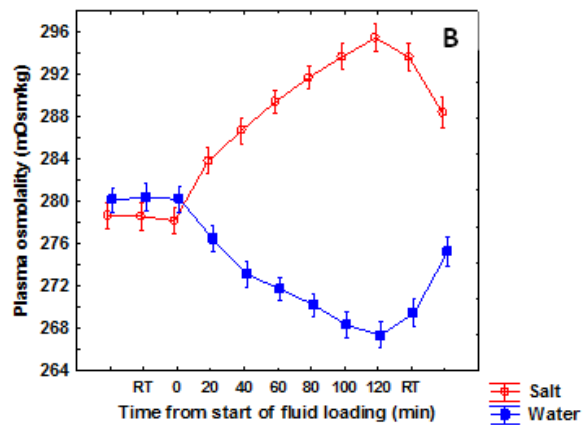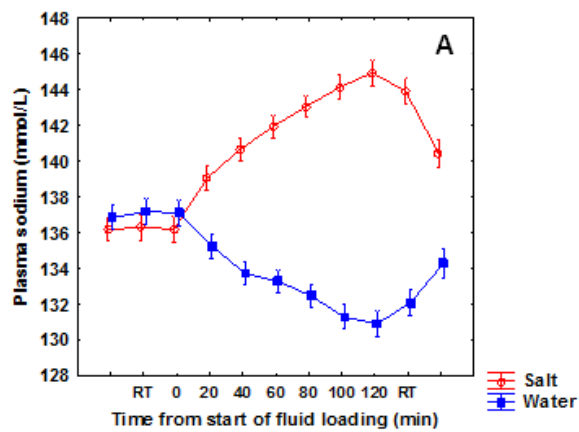
Figure 1. Plasma sodium, osmolality, pH, $PaCO_2$, base excess, and strong ion difference during the observation time

A) Decrease in plasma sodium at 120 minutes compared to baseline during water loading ($p<0.001$). Increase in plasma sodium at 120 minutes compared to baseline during salt loading ($p<0.001$).

B) Decrease in plasma osmolality at 120 minutes compared to baseline during water loading ($p<0.001$). Increase in plasma osmolality at 120 minutes compared to baseline during salt loading ($p<0.001$).

C) Lowest pH at 80 minutes compared to baseline during water loading ($p=0.14$). Lowest pH at 120 minutes compared to baseline during salt loading ($p<0.001$).

D) Decrease in $PaCO_2$ at 80 minutes compared to baseline during water loading ($p=0.002$). $PaCO_2$ at 120 minutes compared to baseline during salt loading ($p=0.65$).

E) Decrease in BE at 80 minutes compared to baseline during water loading ($p<0.001$). Decrease in BE at 120 minutes compared to baseline during salt loading ($p<0.001$).

F) Decrease in SID at 80 minutes compared to baseline during water loading ($p<0.001$). Decrease in SID at 120 minutes compared to baseline during salt loading ($p<0.001$). Salt; Salt loading. Water; water loading, BE; base excess, SID; strong ion difference, RT; rebreathing test. Bars represent mean ± 95% confidence interval.

Paper 2 Hyponatraemia during labour

We included 308 women in the study, but 21 women were later excluded as blood sample analyses were incomplete. Data from 287 women are included in the results (125 nulliparas and 162 multiparas). Baseline values regarding age, weight, plasma sodium, and plasma osmolality were similar in all groups. For details, see study 2.

Sixteen women (26 %) of those who received more than 2.5 liter of fluids during labour developed hyponatraemia ≤130mmol/L, with a mean reduction (SD) of plasma sodium 6.7 (2.7) mmol/L. Reduction in plasma sodium was significantly correlated to the duration of labour and to total fluid volume administered during labour (Fig 2), but not to hourly fluid intake (p=0.16). Roughly two thirds of all fluids were administered orally, the remaining third was administered intravenously (Figures 3 and 4). Calculated total hourly fluid volume was approximately 300 milliliter per hour and was similar in all women (p=0.16), with exception for those with shorter lasting labours. However, hourly intravenous infusion volumes were higher in hyponatraemic women (p<0.001). Analysis by multivariate logistic regression showed that maternal hyponatraemia was significantly correlated with total fluid volume administered during labour (p<0.001), but not with OT administration (p=0.072), or with epidural analgesia (p=NS).
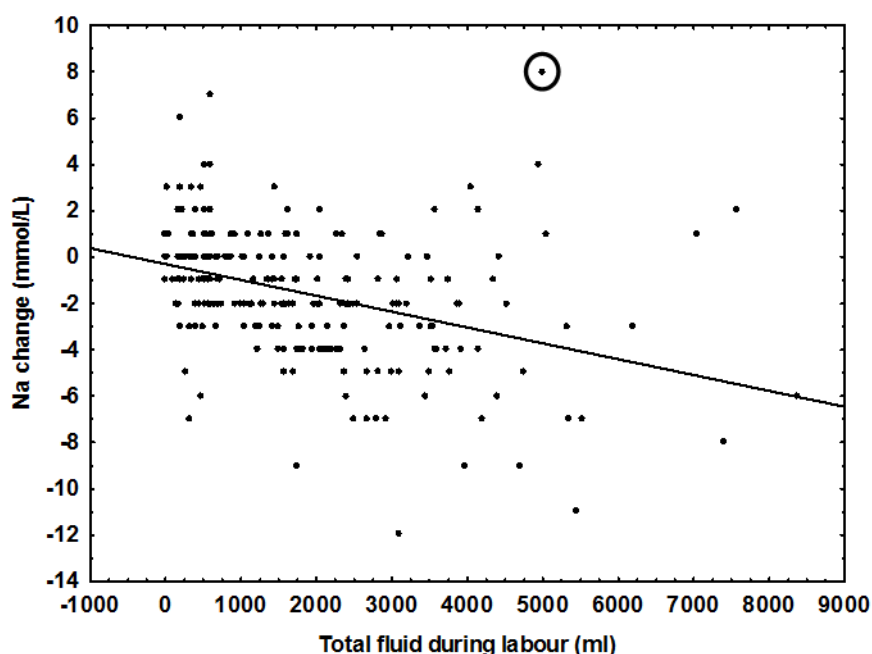

Figure 2.Plasma sodium after delivery correlated to fluids during labour. Reduction in plasma sodium was significantly correlated to total fluid volume (p<0.001). One woman with increased plasma sodium despite high fluid intake is indicated with **O.** Na change; maternal plasma Na change during labour.
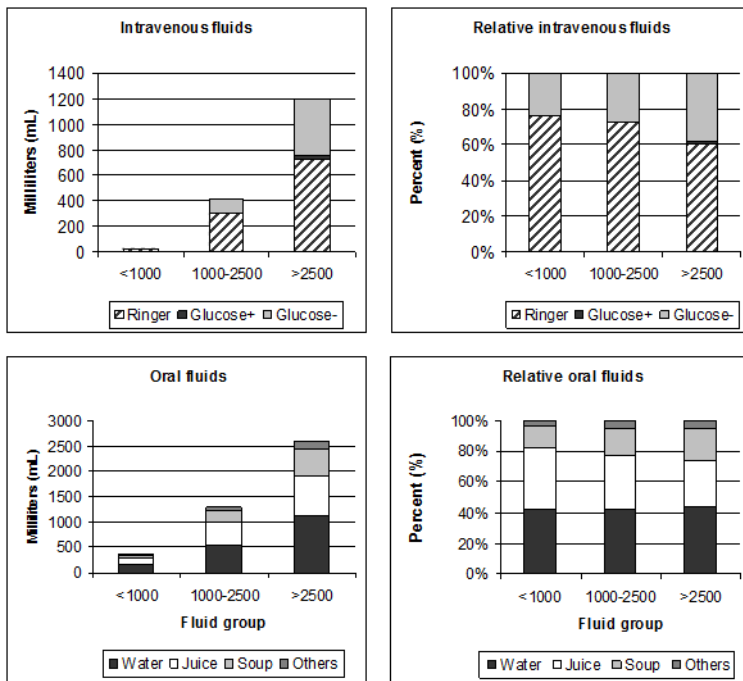
Figure 3.Oral and intravenous fluids during labour in the three fluid groups (mean values used). Mean sodium content of intravenous fluids was 69 mmol/L. In addition to the 130 women who received oxytocin intravenously, 93 women received Ringer's acetate during neuraxial analgesia, and 22 women received caloric supplement as glucose 50 or 100 mg/ml. Sport drinks are included amongst oral fluids called "others". Ringer: Ringer´s acetate, Glucose +: Glucose 50 or 100 mg/ml with Na 50 mmol/ L, Glucose-: Glucose 50 or 100 mg/ml without electrolytes.
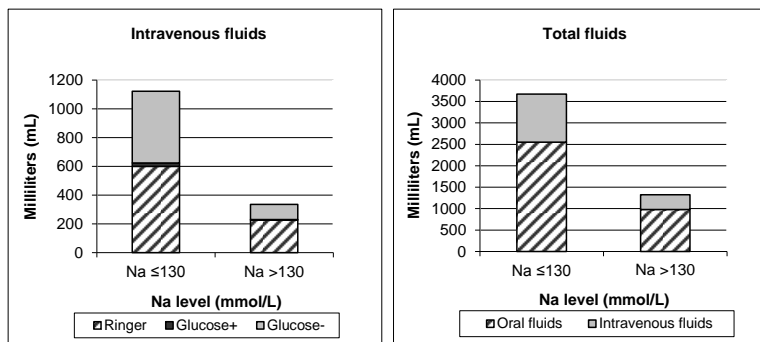
Figure 4. Fluids related to maternal hyponatraemia ≤130 mmol/L. Hourly oral fluid intake was similar in all women (p=0.7). Glucose was administered intravenously as energy supply to 22 women, of these 8 women developed hyponatraemia ≤130 mmol/L after having received a mean of 600 milliliter (range 100-1500 milliliter). Ringer: Ringer´s acetate, Glucose +; Glucose 50 or 100 mg/ml with Na 50 mmol/L. Glucose-; Glucose 50 or 100 mg/ml without electrolytes. Mean values used.
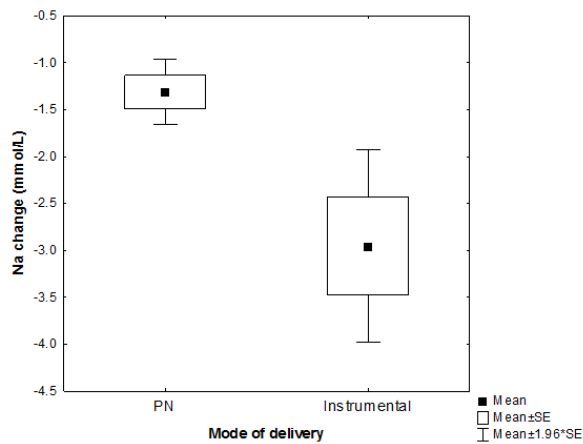
Figure 5. Spontaneous vaginal delivery versus instrumental delivery. Na change; maternal plasma Na change during labour, PN; vaginal delivery, Instrumental; vaginal instrumental delivery or caesarean section with indication failure to progress.

Maternal reduction in plasma sodium correlated with longer duration of second stage, instrumental delivery, and emergency caesarean for failure to progress (p< 0.001, Fig. 5).Umbilical arterial sodium concentration showed significant correlation with postpartum maternal values (p < 0.001), and was higher than maternal levels, mean difference (SD) 2.8 (2.9) mmol/L.

## Paper 3 Hyponatraemia and myometrial contractility

Seventeen women age (SD) 34.9 (4.5) years participated in the study. Mean BMI was 24.4 (5.7) kg/m^2. Ten women had previously been delivered by caesarean section. For further details see study 3.

First part of the study: isolated effect of hyponatraemia

Bi-or multiphasic contractions increased from 8% to 18%, (p=0.001), and the frequency of contractions also increased, mean increase (SD) was 5.6 (4.2) in the hyponatraemic solution S (p=0.018). Amplitude decreased in three specimens, but we found no significant decrease in the whole group (p=0.09). AUC increased significantly in S (p=0.018). All changes were reversible in solution C (Figure 6). Phase portrait plots are shown in Figure 7.
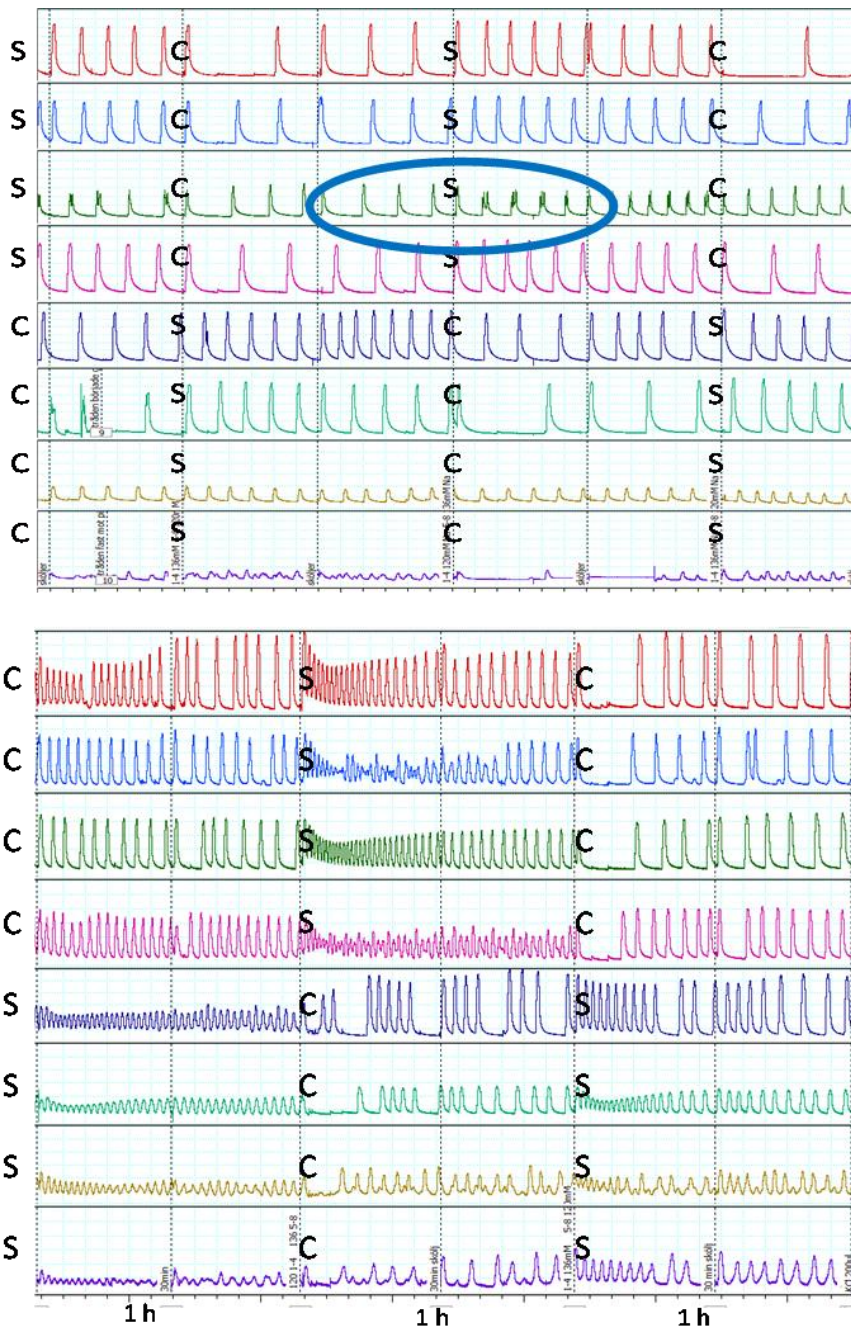
Figure 6. Isometric contraction curves from two different biopsies. Upper panel: Area with appearance of multicomponent contractions indicated. Bottom trace is excluded from analysis due to technical problems. C; normonatraemic control solution with sodium136 mm/L, S; hyponatraemic study solution with sodium 120 mmol/L, 1h;1 hour observation time in each solution.

Second part of the study: combined effect of hyponatremia and oxytocin

Initial multicomponent contraction patterns following OT increased with higher concentrations of OT and were more often observed in solution S. Significant difference between S and C after OT 0. 01 IU/ml (p = 0. 05), and after 0. 1 IU/ml (p =0. 015).

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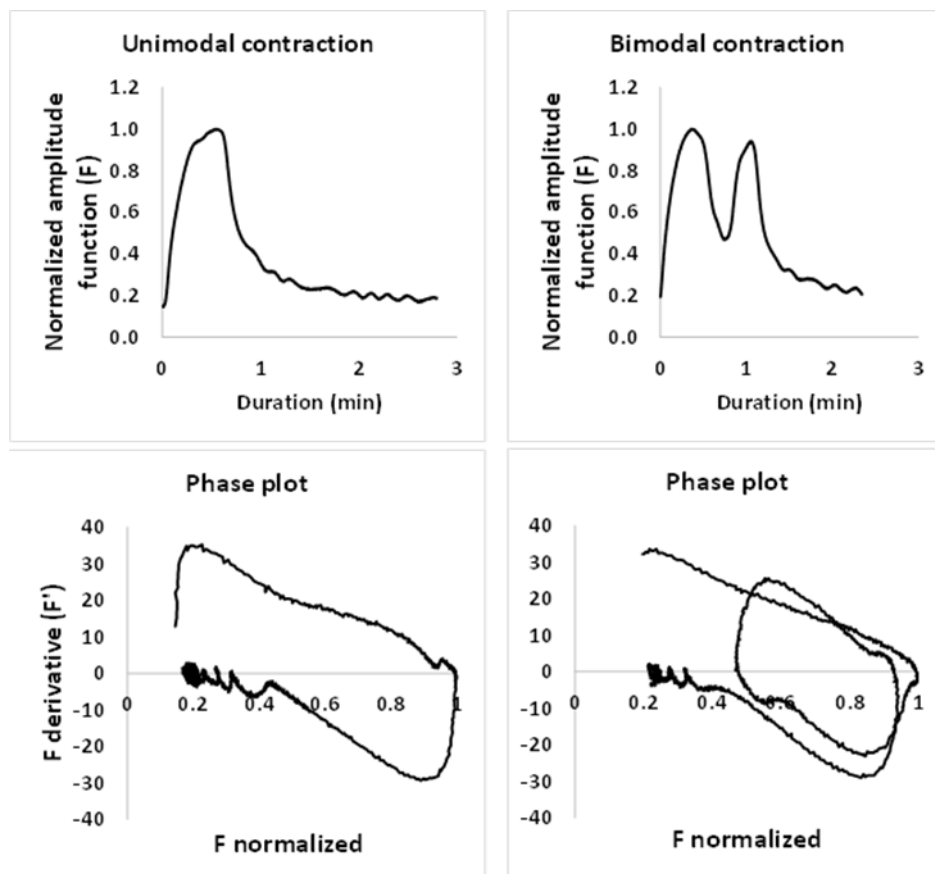
Figure 7. Phase portrait plots of one smooth and one biphasic contraction curve. Left panels: Monophasic, smooth contraction curve with its phase portrait plot. Right panels: Biphasic contraction curve with its phase portrait plot.

Paper 4 Feto-maternal osmotic relationship

Data from 30 women and their newborn were included in the study. Maternal age (SD) was 32.4 (5.5) years, BMI was 29 (4.5) kg/m^2. Caesarean section was performed at gestation weeks 38.8 (0.3). Infants´ weight was 3432 g (357), Apgar at 1 minute 9.3 (0.6), umbilical artery pH 7.3(0.1). For further details see study 4.

Maternal osmolality was (mean; 95% confidence interval) 287.0 (285.8-288.2) mOsm/kg, arterial cord osmolality 289.4 (287.9-291.0) mOsm/kg, venous cord osmolality was 287.3 (286.0-288.5) mOsm/kg. The central laboratory showed maternal sodium 137.7 (137.1-138.2) mmol/L, arterial cord sodium 140.2 (139.6-141.0) mmol/L, and venous cord sodium was 138.6 (137.8-139.3) mmol/L. Maternal albumin was 34.2 (33.2-35.3) g/L, arterial cord albumin was 31.6 (30.6-32.7) g/L, venous cord albumin was 32.1 (30.7-33.4) g/L
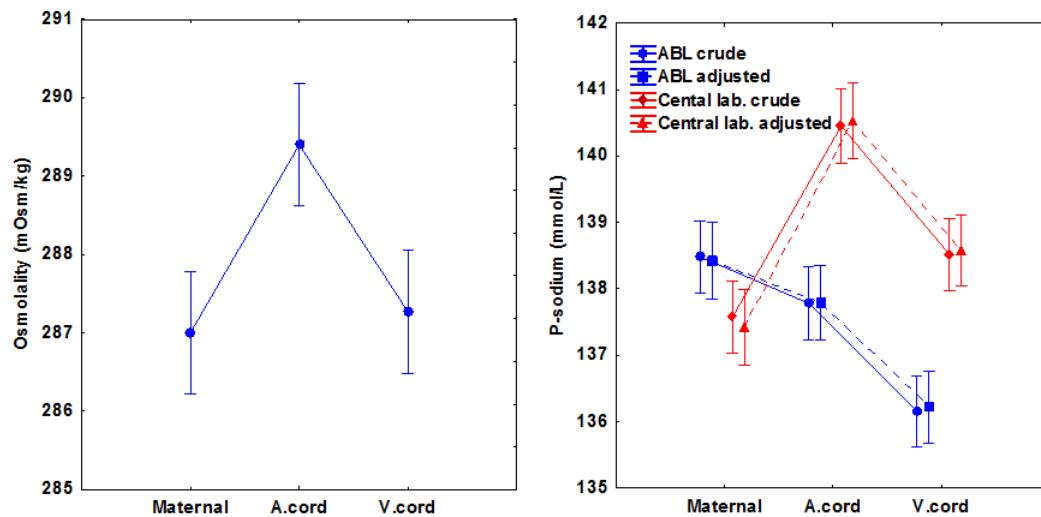
Figure 8. Osmolality and sodium in maternal and cord blood **Left panel**: Osmolality. Difference between maternal and arterial cord, (p<0.001), difference between arterial and venous cord, (p<0.001), difference between maternal and venous cord (p=0.63). **Right panel**: Plasma sodium values from the central laboratory: Difference between maternal and arterial cord, (p<0.001), difference between arterial and venous cord, (p<0.001), difference between maternal and venous cord (p=0.021). ABL sodium is considered incorrect (see Discussion), differences are therefore not calculated. ABL crude; value as reported by ABL, ABL adjusted; value as reported by ABL adjusted for albumin. Central lab crude; value as reported by the central laboratory, Central lab adjusted; value as reported by the central laboratory adjusted for albumin. Correlation between albumin and sodium analysed by the central laboratory: p=NS. Maternal; maternal blood, A.cord; arterial cord blood, V.cord; venous cord blood. The figures show mean values, bars represent ± 95% confidence interval.

We found no differences in chloride between the groups (p=NS), but chloride was 3,4 (2,9-3,9) mmol/L higher when analysed by ABL compared to the values obtained from the central laboratory (p<0.001).
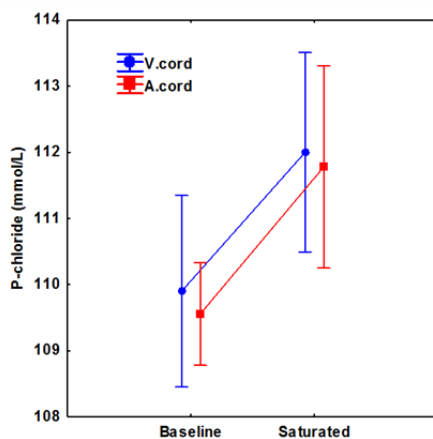
Figure 9. Arterialisation of umbilical cord blood. Baseline; Chloride measured by ABL at delivery. Saturated; Chloride measured by ABL after arterialisation. A.cord; arterial cord blood, V.cord; venous cord blood. Bars represent ± 95% confidence interval

DISCUSSION

Paper 1 Hyponatraemia and breathing

Infusion of hypertonic saline 3% in healthy volunteers caused osmolality to increase and simultaneously hyperchloraemic metabolic acidosis developed. Drinking water caused osmolality to decrease, and a less pronounced metabolic acidosis when compared to salt loading also developed. In both instances metabolic acidosis was caused by a decrease in SID. All changes were similar in men and women, with no difference between the follicular and the luteal phase. However, no respiratory compensation was observed for the metabolic acidosis following infusion of saline, in contrast to respiratory compensation for the lesser metabolic acidosis induced by drinking water. The rebreathing tests showed that sensitivity to CO_2 remained unaltered during both fluid loading procedures, and was therefore not the cause of the absence of respiratory compensation during salt loading. The expected respiratory compensation for metabolic acidosis is usually immediate, and its magnitude can even be predicted.

We interpreted this phenomenon as the human equivalent of respiratory inhibition by increased osmolality observed in animals (39,42). Increased osmolality suppressed thermoregulatory panting in animals, as hyperthermia is preferred to dehydration. Although humans have other means for thermoregulation, our results indicated that the inhibitory effect of increased osmolality on breathing is present also in humans, but without apparent physiological benefit. The mechanisms involved are still unclear, but may include reduction of ANG II and its ventilatory stimulation (23,46) together with increase in AVP that will depress ventilation (48). Animal studies have also indicated possible neurological pathways between the areas of osmosensors and the respiratory center (45).

The respiratory stimulation of lowered osmolality was not evident, as a reduction in $PaCO_2$ was expected as compensation for metabolic acidosis. However, the observation period was short, and towards the end of the observation plasma sodium and osmolality had almost returned to baseline values. Longer duration of hyponatraemia, as in the pregnant woman, could possibly reveal an effect of lowered osmolality as described in previous studies (4,5).

Conventionally, the metabolic acidosis in pregnant women is considered compensation for a primary respiratory alkalosis, in turn induced by progesterone (8), but some studies have interpreted reduction in SID and osmolality as the primary event, and the respiratory alkalosis as secondary (106,107). Our study showed that lowered plasma sodium and osmolality almost immediately caused respiratory alkalosis in men and non-pregnant women, and the same

respiratory response would be expected following pregnancy-induced hyponatraemia. The higher pH often seen in pregnant women compared to our study participants could also be caused by an additional stimulation by the complex hormonal changes in pregnancy.

Paper 2 Hyponatraemia during labour

We prospectively observed 287 women during labour and found that 26% of the women who received more than 2.5 liters of fluid during labour developed hyponatraemia defined as plasma sodium ≤130mmol/L. The mean (SD) reduction of plasma sodium of 6.3 (2.7) mmol/L in these 16 hyponatraemic women showed that hyponatraemia had developed during labour. The lowest maternal sodium was 122 mmol/L, the corresponding plasma sodium of her newborn was 126 mmol/L, fortunately neither developed symptoms of hyponatraemia.

With the exception of women with shorter lasting labours, all mothers included in the study had similar hourly fluid consumption. They drank 200 milliliter per hour, and the combined hourly fluid intake (drink + intravenous infusion) was approximately 300 milliliter, an apparently not exaggerated fluid volume. However, in longer lasting labours the cumulative fluid volume together with a probable increase in AVP caused significant water retention and a consequent reduction in plasma sodium levels.

One study reported approximately 900 milliliter per hour as the maximum capacity of excreting a water load at rest in healthy women, but that this was reduced by one third in late pregnancy (108).

Our results indicated that a maternal fluid overload will partly be transferred to the fetus, and as a consequence, the maternal urine production will be smaller than expected. Maternal fluid loading has also been shown to increase amniotic fluid volume, but only when hypotonic fluid reduced maternal osmolality (109). Hence, the capacity of excreting a water load at rest in late pregnancy could be reduced to a lesser extent than suggested (108).

The women in our study received fluid volumes well below their predicted maximum capacity of renal excretion at rest, therefore the development of hyponatraemia would indicate increased AVP activity during labour. Hyponatraemia during labour caused by OT administered in electrolyte free solutions is well recognised. Despite this, hypotonic solutions are often used as a vehicle for OT, as during our study. However, our multivariate logistic regression showed that hyponatraemia was significantly correlated to fluid volume, but not to OT.

The highest morbidity and mortality rates in hyponatraemic encephalopathy are found in women of fertile age (66,67), considered to be caused by oestrogen induced impairment of the Na^+-K^+ ATPase pump activity in the brain (66). Symptoms of hyponatraemia will probably occur first at a lower level of plasma sodium in the pregnant woman due to the physiological hyponatraemia of pregnancy. Also, images by computerised tomography showed reversible reduction in brain size during pregnancy (110). This could be a result of intracellular adaptation to the reduction of extracellular osmolality.

Liberal fluid intake was probably a combined result of maternal life-style habits and favorable opinion regarding fluid administration amongst obstetricians and midwives. There still is a widespread belief in beneficial effects of abundant water intake, and two obstetric studies quite recent at the time of our study indicated shorter duration of labour following more abundant fluid administration (71,72). A subsequent Cochrane report could not support these findings (73), but cases of even severe hyponatraemia during labour are reported also in more recent years (6,111). Clearly, the potential dangers of exaggerated water intake has not spread to the general public. A leading midwife in Sweden, author of several books and pamphlets, after our study reduced her advice regarding fluid needs during labour from 500 milliliter per hour (74) to 100 milliliter per hour (75). However, nowhere is the risk of water intoxication explained to pregnant women. On the other hand, a general restriction of fluids during labour may prove deleterious for a dehydrated laboring woman. Fluid loss during labour may vary, and sweat, vomit, diuresis due to unrecognised hyperglycaemia, or a rare case of DI, as possibly occurred in one of our study participants, are all conditions that require fluid substitution on an individual basis. Drinking so much as to avoid thirst should not be advocated, and when present, the basic physiological signal of thirst should be satisfied.

The communication of relevant scientific knowledge to the general public could evidently be improved. On the other hand, pregnant women receive much information from sources that are not evidence-based, and health care providers should be aware of the impact this information may have. A bedside registration of fluid consumption during labour would be a simple preventive measure against hyponatraemia. No electrolyte free solutions should be administered, neither for OT, nor for energy supplement. The possibility of significant hyponatraemia should not be forgotten during long lasting labours.

Paper 3 Hyponatraemia and myometrial contractility

In study 2 we found that maternal reduction in plasma sodium correlated with longer duration of second stage of labour, instrumental delivery and emergency caesarean for failure to progress. We therefore addressed the possibility of a causal relationship in study 3. Our in vitro study showed that hyponatraemia caused reversible and significant increase in frequency of contractions without change in amplitude. We also observed significant and reversible increase in bi-and multiphasic contractions in the hyponatraemic solution.

The effect of increased frequency of contractions in spontaneous labour has recently been addressed (112). Previously excessive uterine activity was called "hyperstimulation" as it was most often seen following augmentation with OT. The phenomenon has been renamed tachysystole, and a recent study showed that tachysystole occurred in 11% of spontaneous labours (112). Tachysystole was significantly associated with increased rate of caesarean section, non reassuring fetal heart rate, and admission to neonatal intensive care. Therefore, the increased frequency caused by hyponatraemia could indicate a causal relationship between hyponatraemia and dystocia, explaining the correlation we observed in study 2.

Higher frequency of contractions in the hyponatraemic solution increased AUC, which would conventionally be interpreted as increased contractility. However, recent studies suggested examination of the shapes of isometric contraction curves as an alternative to AUC for determination of contractility. Phase portrait plots were obtained by analysing the traces of force and its first derivate (96,99). The resulting phase portrait plots indicated that contractions following bi-and multiphasic contractions curves could be less effective. We observed a reversible increase in bi-and multiphasic contraction curves in the hyponatraemic solution, and the corresponding phase portrait plots could indicate reduced contractility (Figures 6 and 7). The strips in hyponatraemic solution also more frequently showed initial multicomponent contractions when OT was added in increasing doses. In physiological conditions OT is secreted in a pulsative manner, and several studies have addressed the hypothesis that pulsative administration of OT for induction or augmentation of labour could improve the effect of oxytocin (113,114). A recent large randomised controlled trial showed that pulsative administration of OT for augmentation of labour resulted in longer lasting labours, higher frequency instrumental delivery, and even higher neonatal morbidity, when compared to continuous infusion (115). Our results offer an explanation, as the initial response to OT was more often multiphasic in the hyponatraemic solution, resulting in potentially ineffective contractions.

Paper 4 Feto-maternal osmotic relationship

In study 2 we found that fetal plasma sodium was higher than the corresponding maternal levels. Umbilical arterial sodium was also higher than umbilical venous sodium indicating ongoing equilibration with maternal plasma sodium. Although fetal plasma sodium in the literature is reported equal or lower than maternal levels, neither reviewers nor readers challenged our results. Study 4 was performed to determine the feto-maternal osmotic relationship and also to confirm the feto-maternal sodium relationship we found in study 2. Our previous results were confirmed as we found that fetal plasma osmolality was higher than maternal osmolality due to higher fetal plasma sodium. The placenta is impermeable to vasopressin, and studies have indicated autonomous fetal production and regulation of vasopressin secretion (29,116). Autonomous fetal osmoregulation can explain the creation and maintenance of the feto-maternal osmotic gradient.

Only the plasma sodium values from the central laboratory paralleled the feto-maternal osmotic relationship. The plasma sodium values in cord blood provided by the point of care analyser were erroneous due to preanalytic conditions, explained below.

Our results in studies 1 and 4 indicated that the physiological hyponatraemia of pregnancy caused both a compensatory respiratory alkalosis that favours removal of fetal CO_2, as well as an osmotic gradient that favours water transport to the fetus. This unifying explanation of maternal physiological adaptation and feto-maternal relationship differs from the conventional explanatory model that considers the respiratory alkalosis primary, and the metabolic acidosis compensatory (1), and does not take into account the acidifying effect of hyponatraemia. The application of Stewart´s principles also to analysis of physiological changes of pregnancy would increase understanding and acceptance when Stewart´s principles are applied to study pathological conditions. One recent study showed how analysis according to Stewart-Gilfix could offer predictive information in preeclamptic women (90).

Our findings that maternal albumin was higher than fetal albumin is also in contradiction with the literature (61-63). For pharmacological feto-maternal relationships this albumin gradient is important, and future studies should address our findings.

The chloride ion was for a long time considered the uninteresting counterpart of the more important sodium ion. However, Stewart´s physico-chemical approach to acid-base balance has gained acceptance, and determination of chloride is essential for calculation of SID. The analysis of plasma chloride, once laborious and expensive, is now easily available in everyday clinical practice and also provided by point of care analysers.

We found that plasma chloride was similar in maternal and umbilical arterial and venous blood, in contrast to previously reported higher fetal values (60). We measured chloride in maternal venous blood, whereas maternal arterial chloride would have been even higher due to the well known chloride shift, whereby chlorides entering the red blood cells enhance venous transportation of CO_2 (117). Arterial plasma chloride is therefore approximately 2 mmol/L higher than in venous blood, and when the haematocrit is increased this difference may reach 4 mmol/L. Our arterialised umbilical cord blood samples showed a predictable increase in plasma chloride of 1-5 mmol/L (Fig 9). In conclusion, despite our results indicating the contrary, the content of chloride in fetal blood could be higher than in maternal blood, as previously reported. Plasma chloride will also predictably increase in the newborn following the physiological rise in oxygen saturation after birth. When saline is administered to the newborn in need of resuscitation a resulting hyperchloraemia may contribute to metabolic acidosis, as often described in adults .This introduces an iatrogenic diagnostic bias particularly when lactate is not measured.

Importance of sampling routines

The explanation to our divergent results compared to previous studies may be found in different sampling techniques.

Studies have shown improved neonatal outcome with delayed clamping of the cord (118). This technique has been routine in the labour ward at Kalmar County Hospital for many years and was adopted in study 4. Blood was sampled separately from umbilical artery and vein before clamping of the cord. Previous studies analysed mixed cord blood (62) which consists mainly of venous blood with lower plasma sodium. This could probably explain the lower fetal plasma sodium reported in literature. When analysis is performed on blood sampled after clamping of the cord, the tourniquet effect will within minutes cause a concentration of non-filterable constituents (119). This may explain the higher fetal albumin levels reported in previous studies that analysed blood sampled from the clamped cord.

In study 4 we used heparinised syringes for sampling. The syringes were easily filled with maternal blood, whereas the volume of umbilical cord blood within the syringe usually was less than half. As a consequence, heparin diluted cord blood to a greater extent which caused the point of care analyser to underestimate plasma sodium in umbilical cord blood (120). This source of analytic error was previously described, but unfortunately we were unaware of this effect when we planned the study (121). However, as we also measured osmolality with the

independent method of cryoscopy it was evident that the point of care analyser reported erroneous plasma sodium values.

All values for plasma chloride were higher when analysed with the point-of-care analyser ABL. A previous study reported a discrepancy between chloride values measured by the direct and indirect ISE, but could not explain the difference (121). Both our instruments measured chloride by direct ISE, and the same difference was encountered. The difference of almost 4 mmol/L will cause an underestimation of SID potentially leading to an erroneous diagnosis of hyperchloraemic metabolic acidosis. This should be remembered, particularly when lactate is not measured. It is therefore important to recognise this discrepancy for everyday clinical practice and adjustments should be made according to the local platforms for analysis.

CONCLUSIONS

Study 1

We found that increased osmolality inhibited the expected respiratory compensation for metabolic acidosis in both men and women. In contrast, we observed respiratory compensation for the metabolic acidosis that developed during water loading. As a consequence, it is not evident whether this respiratory stimulation was caused by decreased osmolality, or by metabolic acidosis, or a combination of both. The principal effect of osmolality on ventilation could be that of inhibition when osmolality is increased, but this inhibitory effect could cease at decreased osmolality.

Study 2

We found that hyponatraemia frequently developed during prolonged labour, and that this was caused by ingested or intravenously administered fluids, but unrelated to oxytocin administration or epidural analgesia.

Study 3

Hyponatraemia caused reversible contraction pattern changes in human myometrium. Increased frequency and multiphasic contraction curves could indicate decreased contractility.

Study 4

Our results from study 2 were confirmed, as we found that fetal plasma sodium and osmolality were higher than maternal levels. This osmotic gradient favours water transport to the fetus. Therefore, maternal hyponatraemia exposes the fetus to hyponatraemia that could be aggravated by high fetal AVP levels during prolonged labour. We also found that maternal albumin was higher than fetal albumin, in contrast with previous studies. This may have implications for feto-maternal pharmacokinetics.

CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

The focus of this thesis was to study physiological and pathophysiological events of pregnancy and delivery with special emphasis on osmotic regulation.

Lowered plasma osmolality in pregnant women has been linked to the increased ventilation typical of pregnancy. Our results indicated that the principal effect of osmolality on ventilation could be inhibitory when osmolality is increased, but this inhibitory effect could cease at decreased osmolality. This finding could be of some importance for treatment of patients with retention of CO_2 due to chronic obstructive pulmonary disease. A future study could also address a possible interaction of hyperosmolality on the ventilatory response to hypoxia. A reduced response to hypoxia by hyperosmolality would be of interest in palliative medicine.

We found that fetal osmolality was higher than maternal osmolality, due to higher fetal plasma sodium compared to the pregnancy induced hyponatraemia in the mother. This feto-maternal osmotic gradient has previously not been described. Our results indicated that the physiological hyponatraemia in the pregnant woman caused both a compensatory respiratory alkalosis that favours removal of fetal CO_2, as well as an osmotic gradient that favours water transport to the fetus. Our unifying explanation of maternal physiological adaptation and feto-maternal relationship differs from the conventional explanatory model that considers the respiratory alkalosis primary, and the metabolic acidosis compensatory. This new approach may increase understanding of the complex physiology of the feto-placental unit and pathophysiology of pregnancy, ie preeclampsia.

We also found that acute maternal hyponatraemia quite easily developed during labour. Maternal hyponatraemia could be potentially more damaging for the fetus than for the mother who is adapted to the chronic hyponatraemia of pregnancy. During long lasting labour fetal vasopressin reaches the highest levels measured in humans which could expose the fetus to the risk of hyponatraemic encephalopathy. In the event of fetal ischaemia the interaction with hyponatraemic encephalopathy could aggravate the cerebral consequences of ischaemia. Future studies in this area are warranted. No electrolyte free solutions should be administered during labour, and a bedside registration of fluid consumption would be a simple preventive measure against hyponatraemia.

Our study also indicated that hyponatraemia may negatively affect myometrial contractility, and hyponatraemia might therefore be one of several causes of dystocia. The response to oxytocin might also be altered by hyponatraemia. Future studies should address these findings.

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Pregnant women receive much information from sources that are not evidence-based, and health care providers should be aware of the impact this information may have.

POPULÄRVETENSKAPLIG SAMMANFATTNING

När en kvinna blir gravid genomgår hennes kropp stora förändringar redan innan synlig tillväxt av livmodern. Blodcirkulationen till alla organ ökar så väl som andningsfrekvensen. Illamåendet som drabbar många på morgonen är välkänd, mindre känt är dock att salthalten i blodet sjunker. Man har tidigare ansett att alla dessa förändringar beror på progesteron, ett hormon som utsöndras av äggstockarna. Vissa studier har dock sett samband mellan sjunkande salthalt i blodet och ökad andning.

Sambandet mellan salthalt och andning har studerats hos djur som flåsar för att reglera kroppstemperaturen. Ökad salthalt i blodet uppfattas som hotande vattenbrist, och för att spara på vattnet slutar djur att flåsa, även om det innebär att kroppstemperaturen kan stiga.

I studie 1 undersökte vi om salthalten i blodet påverkar andningen hos människan oberoende av kön. Vi studerade hur andningen ändrades när salthalten i blodet ändrades hos friska försökspersoner. Tio män och nio kvinnor fick vid skilda tillfällen dricka vatten så att salthalten i blodet sjönk, vid andra tillfällen höjdes salthalten genom att de fick saltlösning injicerat direkt in i blodbanan. Vid båda tillfällen blev blodet "surare". Vanligtvis korrigeras denna surhet genom att andningen ökar, och när kolsyrehalten i blodet sjunker minskar också "surheten". Hos våra försökspersoner observerade vi att andningen ökade när surheten orsakades av låg koncentration av salter, men när blodet blev ännu surare av saltlösningen, ökade inte andningen. Människan har alltså behållit kopplingen mellan salthalt i blodet och andning, och det verkar som att hög salthalt bromsar andningen, och att denna broms försvinner när salthalten i blodet sjunker. Lägre kolsyrahalt i den gravida kvinnans blod gynnar transport at kolsyra från fostret.

Förutom den fysiologiska minskningen av salter i blodet hos den gravida kvinnan kan ytterligare minskning av salthalten (hyponatremi) uppkomma under förlossning. Det har under åren rapporterats flera fall av allvarliga komplikationer orsakade av hyponatremim. Vi hade hypotesen att lindrigare fall kunde vara vanligare än vad som tidigare har antagits. I studie 2 observerade vi 287 kvinnor under förlossning. Det visade sig att hyponatremi var vanligt efter långvarig förlossning. Sexton kvinnor som under förlossning fick mer än 2.5 liter vätska utvecklade hyponatremi med plasmanatrium lägre än 130 mmol/L. Statistisk analys visade att hyponatremi var signifikant korrelerad med det totala vätskeintaget. Alla kvinnor fick liknande vätskevolym på cirka 3 deciliter per timme, fördelade på 2 deciliter dryck och 1 deciliter vätska givet som intravenös infusion. Detta förefaller inte vara överdrivet stora vätskemängder, men under långvarig förlossning och med en förmodad ökad unsöndring av vasopressin, ett

stresshormon som också minskar urinproduktionen, kunde hyponatremi utvecklas. Hyponatremi orsakades inte av värkstimulerande medel eller ryggbedövning.

Vi hade också sett att hyponatremi var korrelerat till förlossning med sugklocka eller kejsarsnitt. I studie 3 studerade vi effekten av hyponatremi på mänsklig livmoder genom att ta vävnadsprover från livmodern vid planerade kejsarsnitt. Vi observerade då att hyponatremi orsakade att sammandragningstakten ökade och kontraktionskurvorna blev mer oregelbundna. Dessa förändringar försvann när salthalten återställdes, vilket skulle kunna peka på en sämre sammandragningsförmåga vid hyponatremi. Dessa resultat tyder på att hyponatremi kan vara en av flera faktorer som leder till värksvaghet.

Vid förlossningsstudien undersökte vi salt i navelsträngsblodet direkt efter förlossning och såg då att barnet med få undantag hade högre salthalt i blodet än mamman. Barnets salthalt har tidigare angivits motsvara mammans salthalt, eller lägre. I studie 4 jämförde vi därför igen salthalten i navelsträngsblodet med mammans blod i samband med planerade kejsarsnitt. Vi kom fram till samma resultat som i studie 2, med en högre salthalt hos fostret än hos mamman. Högre salthalt i fostrets blod gynnar vattentransport till det ofödda barnet. Det förklarar också varför fostret kan drabbas av vattenförgiftning om mamman får för mycket vätska under förlossning.

Sammanfattningsvis kan man konstatera att kvinnor under förlossning inte bör dricka eller ges stora mängder vätska intravenöst. Är hon törstig, skall hon dricka, men hon bör inte följa rådet att dricka så mycket att hon undviker att känna sig törstig. Saltfria lösningar bör heller inte ges till kvinnor under förlossning.

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