HYPERNATRAEMIA IN VERY LOW BIRTH WEIGHT INFANTS ADMITTED AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL: INCIDENCE, FLUID MANAGEMENT AND OUTCOME

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DECLARATION

I, Kim Barnard, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics, in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

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On this... 18th day of February 2015

DEDICATION

For

My Husband, Dr Stephen Smith

Without whom this would never have been possible

ABSTRACT

Background: Fluid-management in very-low-birth-weight infants (VLBWI) with hypernatraemia is critical in reducing morbidity and mortality in these infants.

Aim: To determine incidence, fluid-management and mortality-rate in VLBWI with hypernatraemia.

Methods: A retrospective descriptive study. Hospital records of VLBWI diagnosed with hypernatraemia during the first 72 hours of life were reviewed. Data collected included maternal and infant characteristics, type and volume of fluid administered on admission and at diagnosis, environment in which infants were nursed, time to resolution of hypernatraemia and mortality-rate at 28 days of life.

Results: Of the 443 VLBWI born during June-December 2012, 370 files were retrieved, of which 125 infants had hypernatraemia, an incidence of 33.8%. All were started on a sodium-containing fluid on admission, at a volume of 60-110 ml/kg/day. Fluid-increases in response to hypernatraemia were 45-90 ml/kg. Calculation of fluid-increases was based on a formula for water-deficit in 75% of VLBWI. Severity of hypernatraemia was not associated with birthweight (p=0.26), gestational age (p=0.31) or amount of sodium infants were receiving at diagnosis (p=0.58). Common fluid used for correction was 5% dextrose. The correction-rate was fast at >1mmol/hr in 8.4% of patients. The average-time to resolution was 44 hours. The average-time to resolution was longer for infants nursed in an incubator compared to a radiant warmer (49.7 vs. 37.7 hours, p=0.037) and in those nursed under phototherapy (45.6 vs. 40.8 hours, p =0.031). The mortality-rate at 28 days was 22.5%.

Conclusion: The incidence of hypernatraemia in VLBWI at Chris Hani Baragwanath Academic Hospital is high. Fluid-management to correct hypernatraemia was appropriate for most infants.

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My supervisor, for his guidance, assistance and support at all times

Dr Stephen Smith, MBBCh, BSc(Hons), BSc

My husband and coach in statistics. For his support at all times

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LIST OF ABBREVIATIONS

ADH	Antidiuretic hormone
CHBAH	Chris Hani Baragwanath Academic Hospital
ELBWI	Extremely low birth weight infant
GFR	Glomerular filtration rate
HELLP	Haemolysis elevated liver enzymes and low platelets
HIV	Human immunodeficiency virus
IWL	Insensible water loss
mmol	millimole
RAAS	Renin-Angiotensin-Aldosterone System
TBW	Total body water
TEWL	Transepidermal water loss
VLBWI	Very low birth weight infant(s)
NHLS	National Health Laboratory Service

1.0 INTRODUCTION

Ongoing advances in neonatal medicine have significantly improved the survival rate of very low birth weight infants (VLBWI).[1] VLBWI are defined as those neonates with a birth weight less than 1500g, and extremely low birth weight infants (ELBWI) as those weighing less than 1000g.[2] Most of the VLBWI are also preterm and therefore these terms are often used interchangeably. VLBWI being preterm are at risk of having fluid and electrolyte disturbances.

Fluid management in preterm infants provides many challenges for the paediatrician and has long been a controversial topic.[3–5] Much of the debate centres around the volume and type of fluid that is appropriate for a preterm infant in order to provide adequate nutrition but not to predispose the infant to complications of excessive fluid such as bronchopulmonary dysplasia, necrotising enterocolitis or patent ductus arteriosus.[3] Knowledge of fluid and electrolyte requirements, as well as renal function in premature infants is important in preventing morbidity and mortality associated with electrolyte disturbances.[3–6]

1.1 Fluid compartments

Fluid and electrolyte requirements for premature infants differ from those of term infants.[7] During early foetal life, 95% of the foetus's body weight is water. As gestation increases, the proportion of total body water decreases, with the proportion being approximately 80% at 32 weeks gestation and 75% at term.[4,6] This total body water (TBW) is distributed between three main compartments, namely: plasma, interstitial and intracellular

compartments.[6] The plasma and interstitial compartments are collectively known as the extracellular fluid compartment which is primarily composed of sodium and water.[8] Newborns, especially those who are born preterm, have more extracellular fluid than intracellular fluid.[4] In the postnatal period there is an acute reduction in the extracellular space.[8] In the first week of life it is normal for healthy term neonates to lose up to 10%, and preterm infants up to 15% of their body weight, and this is mostly all due to water loss.[9] The diuresis that premature infants undergo post delivery is characterised by natriuresis despite having a low glomerular filtration rate (GFR).[3,7] This normal contraction of the extracellular fluid space contributes to the effectively negative water and sodium balance experienced by premature infants during this adaptive phase. [8]

1.2 Renal factors affecting fluid balance in neonates

There are multiple factors affecting fluid balance in the preterm infant, the first of which is renal function.[10] Fluid and electrolyte balance is determined mostly by renal function.[4] Embryonic development of the kidney is a complex process with nephrogenesis starting at about 2-5 weeks gestation, maturation of the nephrons starting between 20-22 weeks gestation and completion of nephrogenesis by 34 weeks gestation. [5,10] Infants born before 34 weeks gestation therefore have continuing formation of new nephrons post-delivery. [5] The GFR is low in preterm infants due to the immaturity of the renal system and in combination with the immature nephrons that are present, means that they have a decreased ability to excrete excess fluid and/or electrolyte loads in the first few days of life.[3,5] As gestational age increases so does renal function mature. [5] Premature infants have high urinary excretion rates of sodium when compared to term infants.[7] As the GFR in premature infants is lower than term infants, the higher sodium excretion rates seen in

premature infants must be explained due to lower tubular reabsorption rate of sodium.[7] The proximal renal tubule reabsorbs most of the glomerular ultra filtrate.[5] Sodium reabsorption in the proximal tubule is regulated by the sodium-potassium-ATPase pump on the luminal membrane.[5] Due to immaturity of the proximal tubule, the proton pump has decreased activity in the neonatal tubule and therefore leads to decreased sodium reabsorption and ultimately also decreased reabsorption of water. [3] The prematurity of the renal tubular system means that a preterm infant has both a limited ability to excrete sodium and is also unable to retain sodium as effectively as term babies do. Post delivery tubular function rapidly matures as does the renal response to regulatory hormones, all of which are mechanisms for sodium homeostasis.[3] However, the Renin-Angiotensin-Aldosterone system (RAAS) in premature infants cannot be appropriately inhibited which means that there is a high risk for sodium overload if high levels of sodium are given.[3] Also, the renal ability to both retain and excrete sodium load is reduced in the premature infant which makes them extremely vulnerable to adverse effects of inappropriate sodium administration in the first few days of life. [8]

Water homeostasis is regulated by either excretion of excess water or conserving it by concentrating the urine. However, in the premature infant the GFR is low which limits the delivery of fluid distally in the tubule.[5] There is also a decreased ability to concentrate urine which in part is due to the blunted response of the collecting duct to antidiuretic hormone (ADH) . [5] Premature infants therefore have higher fluid losses due to increased IWL which is further compounded by renal factors which hinder reabsorption of water, all of which predispose the neonate to dehydration. [3,8]

1.3 Insensible water losses

Another factor contributing to fluid balance is water loss. Water loss in newborns can be due to sensible losses, which are quantifiable (e.g. urine losses, faecal water losses) or insensible losses which are not quantifiable (e.g. water loss through skin or respiration).[4] Sensible losses should make up the majority of loss, but premature and particularly VLBWI, have high insensible water losses (IWL) which can be as high as 200ml/kg/day in some instances.[10–12] Insensible water loss also varies with gestational age - the lower the gestational age the higher the IWL.[13] VLBWI have disproportionately higher transepidermal water losses (TEWL), as they have a relatively large body surface area to weight ratio and their skin is immature as it has an immature stratum corneum and lacks keratin. Keratinisation starts at around 18 weeks gestation but it is not until 34 weeks gestation that the stratum corneum becomes well developed.[8] Unlike renal function, skin maturation is not accelerated by the administration of antenatal steroids, it is accelerated by birth and increasing postnatal age.[8] The immaturity of the preterm infants skin lead to increased water losses via evaporation and convection, which can be precipitated by numerous environmental factors [1,4,6,10,14] Infants younger than 36 weeks gestation cannot sweat - for this reason only water and no sodium is lost through the skin.[8]

Environmental factors that contribute to increased IWL in VLBW premature infants are: nursing infants under radiant warmers, receiving phototherapy or being ventilated with non- humidified oxygen.[6] The highest levels of TEWL occurs in the first few days post-delivery, and those infants less than 28 weeks gestation who are nursed under radiant warmers are the most vulnerable to increased losses.[8] Water is lost from the skin through convection and conduction and when water evaporates from the skin it is accompanied by

the loss of heat.[13,15] A high humidity environment can decrease TEWL, and this can be provided by double walled incubators.[8] Several research papers have suggested that radiant warmers affect IWL more so than incubators, however more recent studies have shown that the TEWL does not differ markedly between non-humidified incubators and radiant warmers.[15] Due to prematurity, these infants are also frequently tachypnoeic or are in respiratory distress which may require ventilation (e.g. nasal continuous positive airway pressure or conventional mechanical ventilation). Tachypnoea in itself increases insensible water loss.[1,4,6] Current evidence is conflicting as to whether or not modern phototherapy units increase TEWL.[3,8] Most paediatricians will increase daily fluid intake by 20ml/kg/day and in an otherwise healthy infant this extra fluid is unlikely to cause any harm.[3]

Aside from increased water losses in premature infants, it should also be recognised that when compared to term infants, VLBWI have increased fluid requirements as well. This is due to the fact that they have a higher metabolic rate which means they have a higher caloric expenditure and ultimately need higher fluid intake to meet this demand.[4,6] Therefore it is often not possible to provide adequate fluid amounts that avoid electrolyte abnormalities or fluid deficit.

1.4 Incidence of hypernatraemia

Hypernatraemia is a common derangement encountered in the management of VLBWI infants.[10,11] Literature varies with regards the definition of hypernatraemia with some defining it as a serum sodium of > 147mmol/L and others as >150mmol/L.[16–18] It is most commonly encountered in the first 72 hours of life.[10] The incidence of hypernatraemia in

VLBWI is not well documented. Harkavy and Scanlon reported the incidence of hypernatraemia in preterm infants as 40% while Gawlowski *et al* reports the incidence as 30%. [10]

1.5 Causes of hypernatraemia

In neonates hypernatraemia is most often due to excessive fluid loss or decreased fluid intake, rather than excess sodium intake.[10,11] Neonates are solely reliant on caregivers for provision of fluid maintenance and caloric requirements, and it is therefore of vital importance to have a thorough knowledge of the fluids administered to these infants. Within any neonatal unit, protocols are in place regarding fluid management, which ensures consistency in the management of VLBWI. An intravenous fluid prescription should take into account water losses through urine plus the estimated insensible water loss of the patient.[8] Starting a patient on a 10% glucose solution is acceptable, but it is suggested that sodium intake should only start once there has been weight loss of approximately 6% of the birth weight.[8] Randomised trials have suggested that early administration of sodium increases the risk of hypernatraemia as well as the risks of respiratory morbidity by hampering the normal contraction of the extracellular fluid space.[8]

Monitoring adequate fluid administration should be undertaken carefully, and this is done by recording birth weight and subsequent weight loss, serum creatinine, sodium and potassium levels as well as measuring urine output from birth.[8] Often overlooked, but also important, is that these neonates get inadvertent sodium loads while admitted, which could contribute to the development of hypernatraemia (e.g. drug administration such as dopamine or dobutamine or from flushing intravenous lines).[6] Daily sodium requirements

are 2-3mmol/kg/day and should not be exceeded.[4] There are two basic defence mechanisms against developing hypernatraemia namely, the ability to produce concentrated urine and the development of thirst.[19] The premature infant however, has an impaired ability to concentrate their urine and are unable to provide for themselves even if thirsty.[4]

1.6 Morbidity and mortality associated with hypernatraemia

The morbidity and mortality associated with hypernatraemia is mostly due to dehydration and the subsequent fluid and electrolyte shifts between compartments. [20] Hypernatraemia leads to an efflux of fluid from the intracellular space into the extracellular space to maintain osmotic balance.[19,21] This shift subsequently leads to temporary cerebral dehydration and cell shrinkage.[19,21] Within an hour, the brain compensates by increasing its intracellular content of sodium, potassium and idiogenic osmoles.[19,21] Within a week the brain would have regained 95% of its water content.[19] If hypernatraemia develops quickly however, the brain may be unable to increase its intracellular solutes sufficiently to maintain its volume.[19,21] The immature brain is fragile and cerebral dehydration from hypernatraemia can lead to physical separation of the brain from the meninges, which leads to rupture of delicate bridging veins and results in intracranial and intracerebral haemorrhages, venous sinus thrombosis and infarction.[19,21] These complications can ultimately lead to severe brain damage, adverse neurodevelopmental outcomes and death.[10,12] Intracerebral haemorrhages may lead to destruction of hypothalamic nuclei which decreases the secretion of ADH, limiting water reabsorption by the kidney and therefore perpetuating the hypernatraemia. [21]

1.7 Management of hypernatraemia

The goal of management of hypernatraemia in preterm infants is to reduce sodium levels by correcting fluid deficit and avoidance of giving extra sodium.[21] The amount of fluid given to correct hypernatraemia depends on its severity and the rate at which the hypernatraemia is corrected. The brain has a relative inability to excrete idiogenic osmoles and therefore too rapid a correction of the hypernatraemia can lead to cerebral oedema and associated seizures.[19,21] It is generally accepted that the rate of correction should be a reduction of serum sodium levels of 0.5mmol per hour or 12 mmol in 24 hours.[19,21]

Correcting the free water deficit is done by calculating the amount of free water needed to reduce the sodium level by 0.5mmol/hour.[17] In the case of severely elevated sodium levels it is apparent that the sodium level may not return to normal values within 24 hours, but it should be understood that the goal of management is to return the level to normal values at a safe rate, not necessarily within a given time. One of the formulas that have been used to calculate amount of extra water to be given to correct hypernatraemia is as follows:

millilitres of free water over 24 hours = 600 x weight (kg) x (1-required sodium/current sodium). [22]

Required sodium would be the serum sodium level you want to achieve over the 24 hour period. Free water fluids are added over and above the usual maintenance requirements of the infant. If daily sodium requirements are already being met by maintenance fluids, a sodium free fluid such as 5% dextrose water is added to correct the hypernatraemia.

1.8 Justification for study

Chris Hani Baragwanath Academic Hospital (CHBAH) provides healthcare services to a large neonatal population, both born at the hospital or referred from surrounding clinics. It is estimated that about 3-5% of deliveries are VLBWI. The proportion of VLBWI who develop hypernatraemia at CHBAH is not known. It is important to know the incidence of hypernatraemia as it is associated with high morbidity and mortality. Information on how these patients are managed will assist in whether to review the current practice on fluid management or not, as changes in fluid management might affect outcomes. Secondly the fluid used for maintenance requirements on day one of life contains sodium, while the recommendation is not to provide sodium to newborn babies on the first day of life. Clinicians managing these infants are often trainees who might under- or overestimate fluid requirements leading to electrolyte disturbances. Underestimation of fluid requirements might result in hypernatraemia. This study would therefore like to determine the incidence of hypernatraemia in VLBWI admitted in CHBAH neonatal unit, as well as document the fluid management and outcome of VLBWI with hypernatraemia.

2.0 STUDY AIMS

The aims of the study were to determine the incidence, fluid management and mortality rate in infants with hypernatraemia and factors associated with its severity.

The objectives of this study were:

- To determine the proportion of VLBWI who develop hypernatraemia (serum sodium $\geq$150 mmol/ L) in the first 72 hours of life in the Neonatal Division at CHBAH
- To determine the amount and type of fluids that the hypernatraemic VLBWI were receiving at time of diagnosis of hypernatraemia
- To determine the amount and type of fluid that the infant was receiving when hypernatraemia resolved
- To determine the time it takes for hypernatraemia to be corrected
- To document mortality rate in infants with hypernatraemia

3.0 METHODOLOGY

3.1 Research question

What is the incidence, fluid management and mortality rate of hypernatraemia in very low birth weight infants born and/or admitted at Chris Hani Baragwanath Academic Hospital?

3.2 Study design

This was a retrospective descriptive study.

3.3 Study site and population

The study was based at the Neonatal Division of Paediatrics at Chris Hani Baragwanath Academic Hospital. All VLBWI born at <37 weeks gestation, who were admitted at CHBAH between 1 June and 31 December 2012, and were diagnosed with hypernatraemia within 72 hours of life were eligible for the study. Very low birth weight infants were defined as infants who were born weighing less than 1500g. Hypernatraemia was defined as serum sodium greater than 150 mmol/L

3.4 Data collection

The medical records of VLBWI with a diagnosis of hypernatraemia were reviewed. Data on maternal demographics, infant characteristics, serum sodium levels, type and amount of fluids infants received at diagnosis and in response to hypernatraemia, as well as the

number of patients who died within the first 28 days of life was collected and recorded in an appropriately designed data collection sheet. (Appendix A)

3.4.1 Maternal demographics

Maternal details were collected from the infant hospital file, as they are recorded on the front page of the file at admission in the form of text or check boxes. Where a check box was not ticked next to a treatment or diagnosis in the mother, it was assumed that the mother did not have the treatment or diagnosis. The following maternal details were collected; maternal age, whether antenatal care was received, gravidity, place and mode of delivery, maternal illness during pregnancy or labour, HIV status and whether antenatal steroids were given or not.

3.4.2 Infant characteristics, diagnosis and outcome

The data included for these infants were birth weight, gestational age, Apgars at 1 and 5 minutes post-delivery, gender, date, time of birth, diagnosis of intraventricular haemorrhage and mortality at 72 hours, and 28 days of life. Gestational ages were obtained from obstetric notes in the form of dates of last menstrual period or from early ultrasound, and in addition all premature babies have their gestational age clinically determined using a Ballard score. The neonates are given gestational age based on sonar if the sonar was done during the first semester and where this is not available, a gestational age from the Ballard score is used.

3.4.3 Environmental factors

Information regarding the infants nursing environment was collected. The information retrieved was related to the environment in which the infant was nursed in the first 72 hours of life. The use of incubator versus (vs.) radiant warmer, need for ventilation in the form of nasal continuous positive airway pressure (nCPAP), conventional mechanical ventilation (CMV) or both as well as the use of phototherapy was recorded.

3.4.4 Type and amount of fluids administered

The type and volume of fluid (ml/kg/day) received by the infant was collected at three time points; at birth, at time of diagnosis of hypernatraemia, and in response to hypernatraemia. The volume received per day included both oral and intravenous fluids. When fluids were adjusted in order to correct the hypernatraemia, it was assessed whether or not the additional fluid was calculated according to the formula, [600 x weight(kg) x {1- desired sodium/serum sodium] or not. Where calculation of fluid adjustment for hypernatraemia was not recorded in patient files, the researcher calculated fluid adjustments to determine whether the formula was used or not. The amount of sodium received by each neonate at birth from their prescribed fluids was calculated (mmol/kg/day) and was stratified in to the following groups; <2.5mmol/kg/day, 2.5-2.99mmol/kg/day and ≥3mmol/kg/day.

In an attempt to determine the amount of fluids administered in response to hypernatraemia, I determined the amount of fluids the patient was on when the bloods showing hypernatraemia were done, and amount of fluids the patient was put on after hypernatraemia was diagnosed.

3.4.5 Diagnosis of hypernatraemia

Blood results with serum sodium were captured from the patients' files. The specimen reference numbers were used to check the times that specimens were received at the laboratory. In order to determine the time it took for hypernatraemia to resolve serum sodium levels were recorded from the first sodium recorded to be >150 mmol/L and all subsequent ones until the serum sodium was <150 mmol/L or patient died.

3.5 Ethical clearance

3.5.1 Permission

Permission to perform the study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (Clearance number M130652) and from the Protocol Review Committee of the CHBAH (appendix C).

3.5.2 Confidentiality

A list which contained the names and hospital numbers of the selected infants was kept confidential by the author. This list was used only during retrieval of the medical records. Entry of data on the collection data sheets and on the computer spreadsheet was coded and anonymous.

3.6 Data processing and statistical analysis

Each patient was allocated a study number. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of the Witwatersrand. REDCap is a secure, web-based application designed to support data capture for research studies.[23] Means and standard deviations were used to describe continuous variables with normal distribution. Where continuous variables were not normally distributed, median and ranges were used. Frequencies and percentages were calculated for categorical variables. Comparisons were done using Pearson Chi-square test for categorical variables and Student t-test or One Way Analysis of Variants (ANOVA) for continuous variables. All statistical tests were carried out in STATISTICA Version 12 and/or SPSS version 20.

4.0 RESULTS

Four hundred and forty three VLBWI were delivered at CHBAH, between 1 June 2012 and 31 December 2012. Files for 370 VLBWI, born during this period, were retrieved, reflecting an 83.5% recovery rate of files. One hundred and thirty five patients with hypernatraemia were identified but in 10 patients the hypernatraemia was diagnosed after 72 hours of life and were therefore excluded. A further 5 patients were excluded from statistical analysis as the details regarding fluid management were missing from the files. These five patients were however used in the calculation of incidence as they met the inclusion criteria, but not in further analysis of the data. In summary 125 patients were included to calculate the incidence but only 120 were included for further analysis.

4.1 Incidence

Among the 370 files retrieved, 125 infants were identified to have hypernatraemia. Of the 125 VLBWI, 30 (24%) had a birth weight of <1000g (ELBWI) and 95 (76%) had birth weights between 1000g - 1499g. The overall incidence of hypernatraemia in this cohort of VLBWI was 33.8% (Figure 4.1).

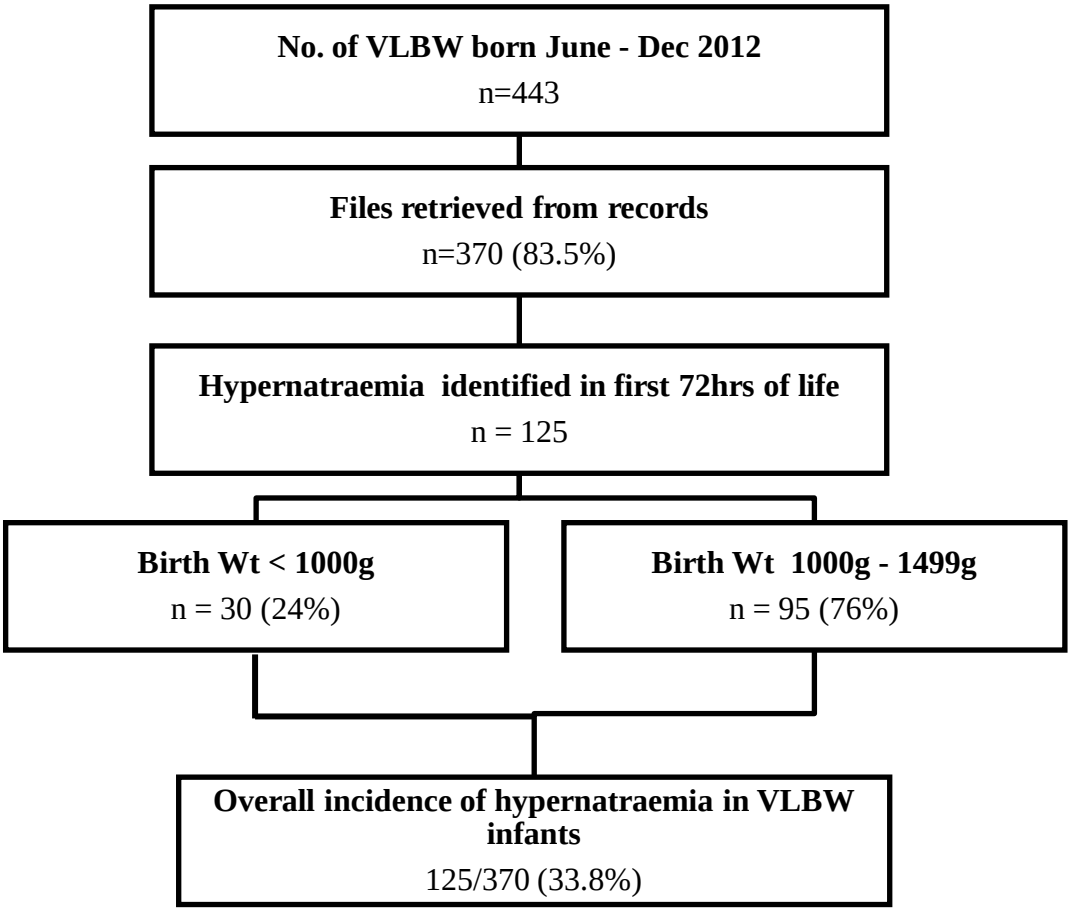

Figure 4.1 Incidence of hypernatraemia in VLBWI at CHBAH

4.2 Maternal demographics

Characteristics of mothers who gave birth to VLBWI with hypernatraemia are illustrated in Table 4.1. The average maternal age was 27 years. The majority of mothers (86.6%) attended antenatal care and were negative for human immunodeficiency virus (72.5%). Majority of mothers (71.7%) had no recorded illness in the antenatal period and 25.8% had a diagnosis of hypertension and/ or HELLP syndrome. Antenatal steroids were only administered to 30% of mothers of VLBWI.

Table 4.1 Maternal characteristics of VLBWI with hypernatraemia

Characteristics	Number (%)
Maternal Age	26.87 ± 6.58*
Antenatal Care	
Yes	104 (86.6)
No	16 (13.3)
Place of Birth	
CHBAH	108 (90.0)
Clinic	8 (6.67)
Home	4 (3.33)
Mode of Delivery	
Vaginal	47 (39.2)
Caesarean section	72 (60.0)
Unknown	1 (0.83)
Gravida	
1	41 (34.2)
1 - 3	55 (45.8)
> 3	17 (14.2)
unknown	7 (5.83)
Maternal Illness	
None	86 (71.7)
Hypertensive disorders	31 (25.8)
Other	3 (2.50)
HIV	
Positive	32 (26.7)
Negative	87 (72.5)
Unknown	1 (0.83)
Antenatal Steroids	
Yes	36 (30.0)
No	84 (70.0)

*- values given as means± standard deviation

4.3 Infant characteristics

The infant characteristics are summarised in Table 4.2. Almost all VLBWI admitted into the Neonatal Division were delivered at CHBAH (90%) and the majority were delivered through caesarean section (60%). The distribution of VLBWI across gender was fairly similar with 49.2% being male and 50.8% being female. The mean gestational age was 29 weeks with the majority (69%) falling between 26-30 weeks gestational age. Majority

(75.8%) of VLBWI had a birth weight between 1000g and 1499g. Just over 50% of infants had an Apgar score <7 at 1 minute compared to 22% at 5 minutes.

Table 4.2 Characteristics of VLBWI with hypernatraemia

Characteristics	Number (%)
Gender	
Male	59 (49.2)
Female	61 (50.8)
Gestational Age (weeks)	29.3 ± 2.5*
<26	4 (3.30)
26 - 28	48 (40.0)
29 - 30	35 (29.2)
31 - 34	31 (25.8)
> 34	2 (1.66)
Birth Weight	
<1000 grams	29 (24.2)
1000 – 1499 grams	91 (75.8)
Apgar 1 min	
<4	19 (17.0)
4-6	40 (35.7)
7-10	61 (54.5)
Apgar 5 min	
<4	12 (10.7)
4-6	13 (11.6)
7-10	95 (84.8)

*values given as means ± standard deviation

4.3.1 Serum sodium levels in infants with hypernatraemia according to birth weight and gestational age

The median sodium level at diagnosis of hypernatraemia in those VLBWI with a weight of <1000g was 153mmol/L (range 150 - 159mmol/L) and in those with a birth weight between 1000-1499g the median was 152mmol/L (range 150 - 197mmol/L) (Figure 4.2). There were no statistical significant differences in levels of serum sodium at diagnosis of hypernatraemia between the two weight categories (p=0.26). Using a one way ANOVA to

compare the serum sodium amongst the different gestational age groups also did not show statistical significant differences (p=0.31) (Figure 4.3). The median serum sodium levels were 152mmol/L (range 150-197), 153mmol/L (range 150-157) and 153mmol/L (range 150-182), for infants receiving sodium of <2.5, 2.5-2.99 and ≥3.0mmol/kg/day respectively (Figure 4.4). A one-way ANOVA showed no statistical difference in the level of hypernatraemia between the three groups (p=0.58), suggesting that the differences in amounts of sodium the infants were receiving at diagnosis did not impact on the severity of the hypernatraemia.

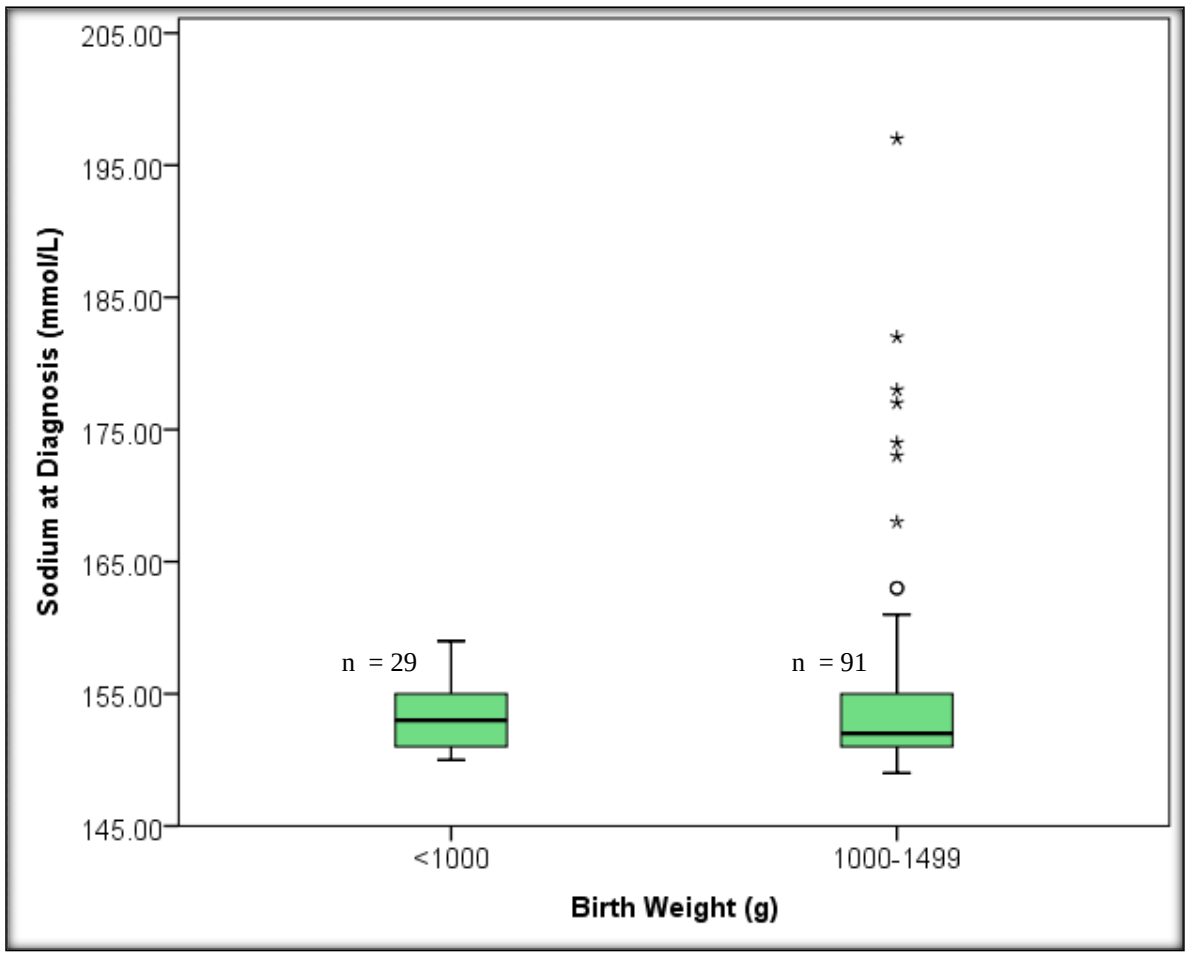

Figure 4.2 Serum sodium across the different weight categories at time of diagnosis

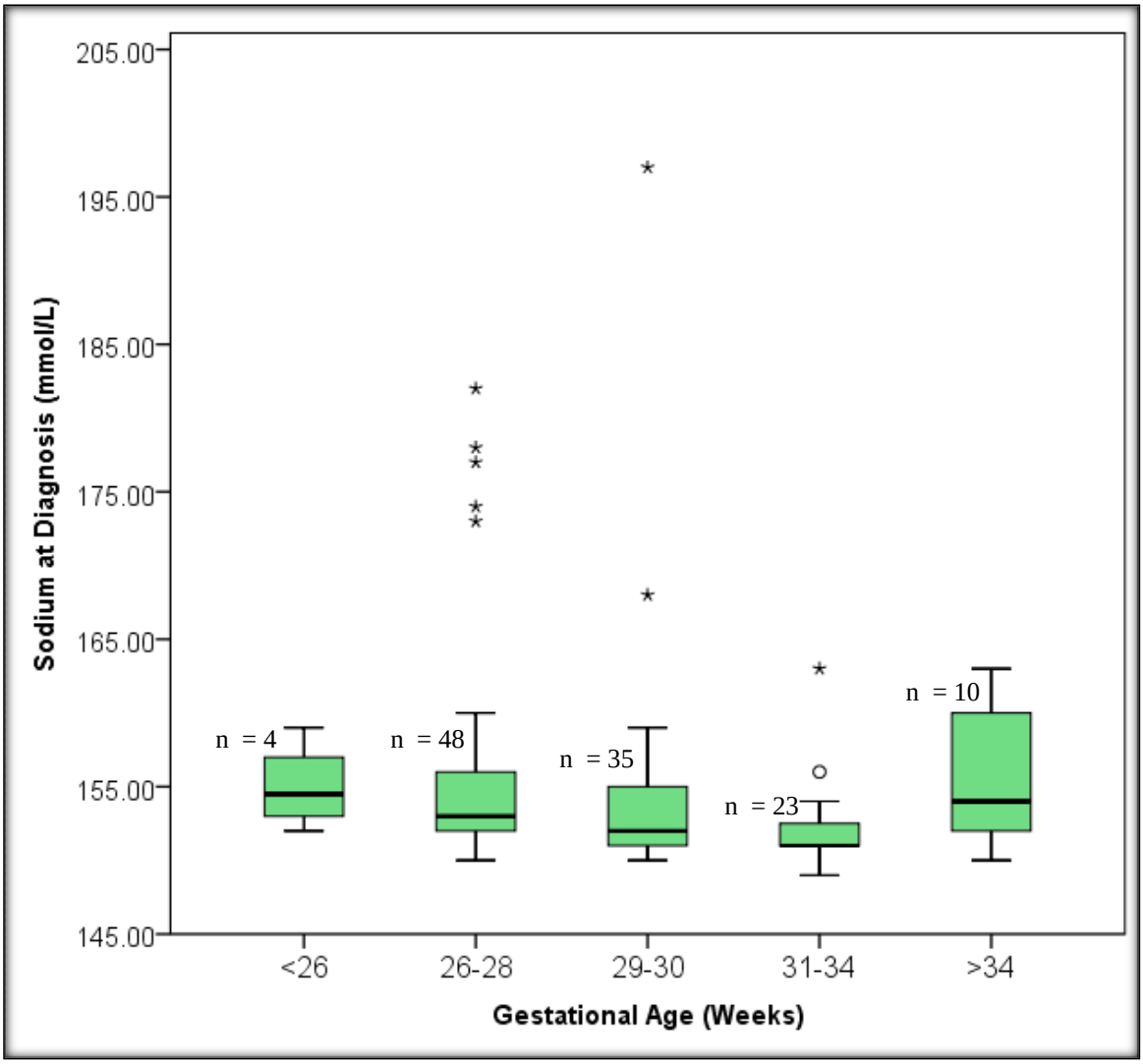

Figure 4.3 Serum sodium levels across gestational ages at time of diagnosis

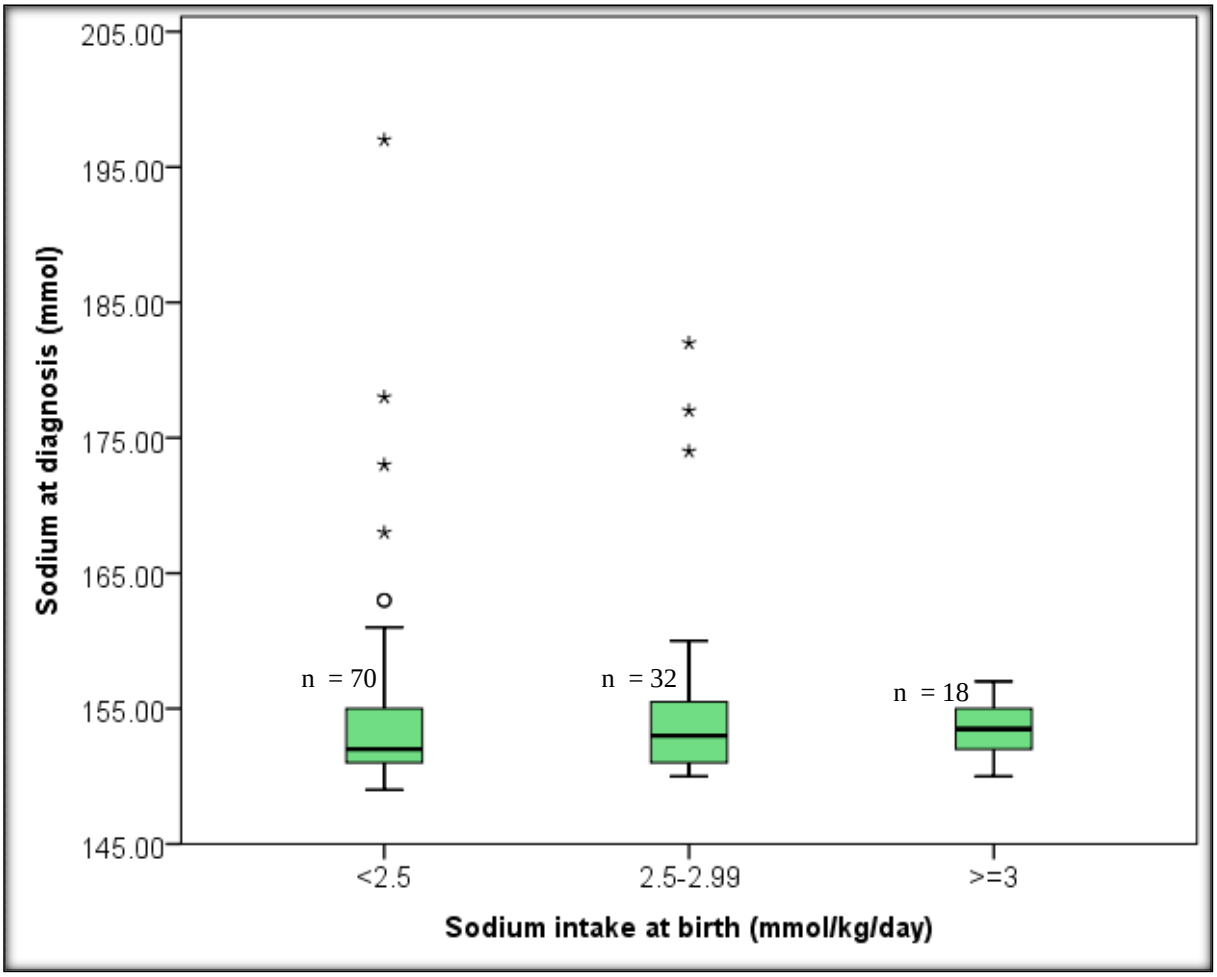

Figure 4.4 Serum sodium levels in relation to amount of sodium the infants were receiving at diagnosis

4.3.2 Total fluid management prescribed at birth (ml/kg/day)

The majority of infants were kept nil per mouth on day one of life and received their fluids intravenously. The fluid prescribed at birth was Potassium-free Neonatalyte, which contains 33 mmols of sodium per litre. The median amount of fluid prescribed across the two weight groups was 80ml/kg/day with the ranges being between 60 - 110ml/kg/day (Table 4.3). With regards the gestational age groups, all groups had a median fluid volume of 80ml/kg/day except for those VLBWI with gestational ages of <26 weeks, whose median was 87.5ml/kg/day of fluid.

Table 4.3 Total amount of fluids infants were receiving at time of admission stratified according to birth weight and gestational age (ml/kg/day)

	Volume (Median) ml/kg/day	Volume (Ranges) ml/kg/day
Birth Weight		
< 1000g (n=29)	80	75 - 100
1000g - 1499g (n=91)	80	60 - 110
Gestational Age		
<26 wks (n=4)	87	80 - 100
26 - 28 wks (n=48)	80	70 -100
29 - 30 wks (n=35)	80	70 - 100
31 -34 wks (n=31)	80	60 - 110
> 34 wks (n=2)	80	80 - 80

4.3.3 Prescribed fluids at time of diagnosis of hypernatraemia

At time of diagnosis of hypernatraemia the ranges of fluid across all birth weight and all gestational ages were between 80 - 167 ml/kg/day (Table 4.4).

Table 4.4 Total amount of fluids the infants were receiving at time of diagnosis of hypernatraemia

	Median Volume (ml/kg/day)	Ranges (ml/kg/day)
Birth Weight		
< 1000g (n=29)	120	80 - 160
1000g - 1499g (n=91)	105	80 - 167
Gestational Age		
<26 wks (n=4)	125	80 - 130
26 - 28 wks (n=48)	120	80 - 162
29 - 30 wks (n=35)	110	80 - 160
31 -34 wks (n=31)	100	85 - 167
> 34 wks (n=2)	94	88 - 100

4.3.4 Fluid management in response to hypernatraemia

The diagnosis of hypernatraemia was made within the first 72 hours of life with two infants being diagnosed on day 1 of life, 72 on day two of life and 46 on day three of life.

Fluids are adjusted based on the level of hypernatraemia. Most of these patients had serum sodium levels between 150-154mmol/L (n=84) with only seven patients having high levels of between 165-170mmol/L. In the first group, the median total fluids were 114ml/kg/day, with a range of 80-167ml/kg/day (Table 4.5). Fluids were increased by an average of 45ml/kg (range: 0-100ml/kg). In the latter group, the median fluid at time of diagnosis was 120 ml/kg/day with an increase in fluids by 90ml/kg (range: 0-170ml/kg). It can be seen that the higher the sodium level, the more fluid was added to the already existing fluid prescription.

Table 4.5 Adjustments made in fluid volume (median and ranges) in response to hypernatraemia

Serum Sodium	No.	Total fluids at diagnosis (ml/kg/d)	Total fluids after diagnosis (ml/kg/d)	Amount fluids increased by (ml/kg)
150-154 mmol/L	84	114 (80-167)	160 (85-222)	45 (0-100)
155-159 mmol/L	23	107 (80-162)	165 (103-255)	55 (0-75)
160-164 mmol/L	6	104 (85-160)	180 (133-209)	70 (48-92)
165-170 mmol/L	7	120 (100-120)	190 (100-290)	90 (0-170)

The fluid administered for correction of hypernatraemia in 99 patients was 5% dextrose water, and of these, 79 patients had the volume increase calculated according to the formula previously mentioned whereas 20 did not (Table 4.6). Of the remaining patients who did not have their additional fluid volumes calculated according to the formula (n=27), 4 were prescribed Potassium-free Neonatalyte and 3 were given Neonatalyte. Fourteen patients had no adjustments made to their fluids.

Table 4.6 Distribution of patients who had fluids increased according to method used to calculate volume and type of fluid used to correct hypernatraemia (n=106*/120)

Type of fluid used to correct in addition to Maintenance fluid	Number of Patients with volume increase calculated according to formula n (%)	Number of Patients with volume increase not according to formula n (%)	All patients who were started on fluids to correct hypernatraemia
Fluid with no sodium (Dextrose water)	79 (78)	20 (22)	99
Fluid with sodium, 33 mmol/L (Potassium free Neonatalyte)	0	4 (100)	4
Fluid with sodium, 20 mmol/L (Neonatalyte)	0	3 (100)	3
Any fluid used	79 (75)	27 (25)	106

*-Fluids not adjusted in 14 infants

The average time taken for the hypernatraemia to resolve was 44.1 hours. Those infants whose fluids were calculated according to the formula resolved within 43.6 hours and those where the formula was not used resolved in 45.1 hours (Table 4.7). A Pearson chi-squared test showed no statistical difference in the time to resolution between the two groups (p=0.57). Fourteen of the infants never had any adjustments made to their

prescribed fluids when the hypernatraemia was diagnosed, one patient had no repeat blood specimens taken therefore couldn't be included in rate calculations and 6 patients died prior to resolution.

Table 4.7 Rate of correction (hours) of hypernatraemia according to method used to calculate fluid volume (n=99*/120)

Hours (h) to resolution	Formula n (%)	No Formula n (%)	Total n (%)
< 24 h	3 (4.11)	0 (0.00)	3 (3.03)
24-48 h	31 (42.4)	12 (46.1)	43 (43.4)
49-72 h	25 (34.2)	9 (34.6)	34 (34.4)
73 – 96 h	10 (13.7)	3 (11.5)	13 (13.1)
> 96 h	4 (5.48)	2 (7.69)	6 (6.06)
Average hours to resolution	43.6 ± 25.92	45.1 ± 36.24	44.1 ± 28.80

*Fluids not adjusted in 14 patients, 6 patients died prior to resolution and 1 patient had no repeat bloods taken and was not included in rate calculations

Rate to correction was also calculated in mmol per hour decrease in the sodium level. The time that the specimen was received at the lab as well as time the specimen was received once hypernatraemia resolved was used to extrapolate the mmol/hour rate of sodium decrease. Thirteen patients could not be included in calculating the rate of decrease of the serum sodium as there were no recorded times for specimens received or only had one blood result. The average rate of correction when the formula was used was 0.28mmol/hour, when no formula was used it was 0.57mmol/hour, and with no fluid added it was 0.39mmol/hour (Table 4.8, Figure 4.5). The average times for correction was therefore slower than recommended in the formula group and within recommended time

for the non formula users. However, a Pearson chi-square test showed no statistical significance in the rate of resolution of the hypernatraemia in mmol/hour between the groups. (p= 0.22).

Table 4.8 Rate of correction (mmol/hour) of hypernatraemia according to method used to calculate fluid volume (n=107* /120)

Rate of correction of hypernatraemia (mmol/ hr)	Formula n (%)	No Formula n (%)	Fluid not adjusted n (%)	Total
< 0.5	58 (80.6)	20 (86.9)	9 (75.0)	87 (81.3)
0.5 - 1	10 (13.9)	0 (0.00)	1 (8.33)	11 (10.3)
≥ 1	4 (5.56)	3 (13.0)	2 (16.7)	9 (8.41)
Average rate of correction	0.28 ± 0.28	0.57 ± 0.58	0.39 ± 0.42	0.41 ± 0.43

*- Rate of correction not calculated for infants who demised with only a single blood result being taken (n=4), infants who didn't have times that specimens were received at the lab recorded (n=8) and the infant who did not have repeat results (n=1)

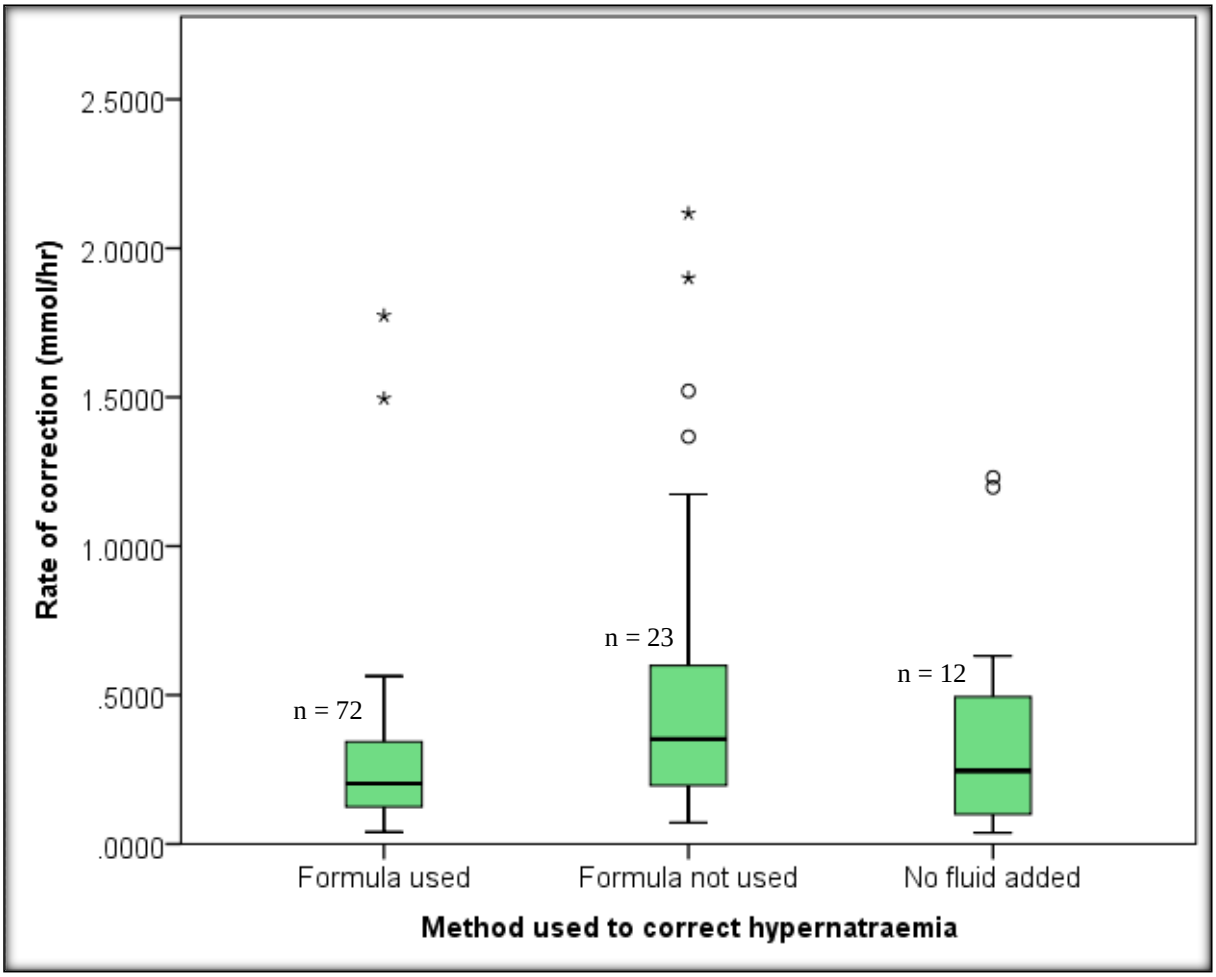

Figure 4.5 Rate of correction of hypernatraemia (mmol/hour) according to method used to calculate fluid volume increases

4.4 Environmental factors

Just over half of infants (55.8%) were nursed in an incubator while the rest were nursed under a radiant warmer (Table 4.9). The mean sodium level in those infants nursed in an incubator was 153.8 mmol/L, and in those under radiant warmer it was 155.5mmol/L. There was no statistical significant difference in the severity of hypernatraemia between these two environmental factors (p=0.16).

There were 66 infants who were started on phototherapy for jaundice in the first 72 hours of life - 35 were nursed in an incubator and 31 under radiant warmer while receiving the phototherapy. There were also no statistical significant differences in the levels of serum sodium in those infants receiving phototherapy whether they were nursed in an incubator or nursed in a radiant warmer (p=0.31).

Table 4.9 Environment under which infants were nursed at time of diagnosis of hypernatraemia and serum sodium levels

	n (%)	Serum Sodium (mean ±SD)
Incubator		
With Phototherapy	35 (52.2)	153.6 ± 4.52
Without Phototherapy	32 (47.8)	153.9 ± 5.92
Radiant warmer		
With Phototherapy	31 (58.5)	155.4 ± 9.06
Without Phototherapy	22 (41.5)	155.8 ± 8.06

The mean number of hours to resolution of hypernatraemia when nursed in an incubator was 49.7 hours vs. 37.7 hours when nursed under a radiant warmer (Table 4.10). The resolution of hypernatraemia was significantly faster when patients were nursed under a radiant warmer (p = 0.037). There was no statistical difference between the total fluid volume infants were receiving (p=0.85) or in the severity of hypernatraemia (p=0.16) between those infants nursed in an incubator and those nursed in a radiant warmer, which could have accounted for the difference in time to resolution

Those patients who received phototherapy took 47.0 hours for their sodium levels to return to normal, whereas those that did not receive phototherapy resolved in 41.1 hours and this difference was statistically significant (p= 0.031) (Table 4.10)

Table 4.10 Effect of radiant warmer or incubator on time to resolution of hypernatraemia

	Hours to resolution Mean ± Std Dev
Incubator	49.7 ± 33.4
Radiant Warmer	37.7 ± 20.2
Received phototherapy	47.0 ± 34.1
No phototherapy	41.0 ± 20.6

4.5 Morbidity associated with hypernatraemia with a focus on occurrence of intraventricular haemorrhage

Cranial ultrasounds were done on 47 of the VLBWI with hypernatraemia. Of these, 31 infants had no IVH, three had Grade 1, six had Grade 2 and seven had Grade 3 IVH. (Table 4.11)

Table 4.11 Finding of IVH in patients with hypernatraemia who had cranial ultrasound done

	Number	Percent
No IVH	31	64.6
Grade 1	3	6.25
Grade 2	6	14.5
Grade 3	7	14.6
Grade 4	0	0.00

4.6 Outcomes within the first 28 days of life

The all-cause overall mortality rate by 28 days of life amongst VLBWI who had been diagnosed with hypernatraemia was 22.5% (n=27). Of these, five died within the first 72 hours, 10 died between 72 hours and less than 7 days and 12 died between 7 and 28 days. Of note is that six patients demised before the hypernatraemia was corrected - five of them having had their fluid deficit calculated according to the formula. Three of the patients who died before correction had a sodium level at diagnosis of 151mmol/L, while the remaining three had levels of 150mmol/L, 155mmol/L and 157mmol/L. The causes of death were related to sepsis in three of these patients, nosocomial sepsis in two and type two respiratory failure in one.

The VLBWI infants who died were of smaller weight ($p<0.001$) and lesser gestational age ($p<0.001$) compared to those who survived, but there were no significant differences in serum sodium levels at diagnosis ($p = 0.070$) (Table 4.12).

Table 4.12 Comparison between survivors and non-survivors

	Survivors Median (ranges)	Non-survivors Median (ranges)	ANOVA p-value
Birth Weight (grams)	1190 (810 - 1490)	970 (800 - 1355)	< 0.001
Gestational Age (weeks)	29 (25 - 38)	28 (23 -31)	< 0.001
Serum Sodium at diagnosis (mmol/L)	152 (150 - 182)	154 (150 - 197)	0.07

The postnatal age at which they died was not associated with birth weight (p=0.430), gestational age (p=0.710) or serum sodium levels (p=0.360) at diagnosis (Table 4.13).

Table 4.13 Comparisons among the non-survivors according to postnatal age at time of death

	Demised at < 72hrs Median (ranges)	Demised at 72hrs - 7 days Median (ranges)	Demised at 7 - 28 days Median (ranges)	ANOVA p-value
Birth Weight (grams)	820 (800 - 1355)	973 (865 - 1295)	1005 (890 - 1355)	0.43
Gestational Age (weeks)	27 (25 - 29)	29 (24 - 31)	28 (23 - 31)	0.71
Serum sodium at diagnosis (mmol/L)	152 (150 -155)	154 (150 - 197)	154 (151 -178)	0.36

5.0 DISCUSSION

Very low birth weight infants (VLBWI) are at high risk for fluid and electrolyte disturbances, including hypernatraemia, due to the prematurity of multiple systems that allow for increased IWL.[10–12] Hypernatraemia is an electrolyte abnormality with a reported incidence of 30-40% in VLBWI, usually occurring within the first 72 hours of life, and is associated with high morbidity and mortality in these infants.[10] It is most commonly caused by excessive fluid loss or decreased fluid intake, rather than increased sodium intake, highlighting the importance of fluid management in the first few days of life.[10,11,16,21] A number of environmental factors namely incubators, radiant warmers and phototherapy may worsen this water loss during the first 72 hours of life.[1,4,6] Hypernatraemia alone or the management thereof is associated with certain morbidities and mortality, therefore its management is critical in survival of preterm infants with or without morbidities. In this report I assessed the incidence of hypernatraemia, fluid management and outcomes from a neonatal unit with a large number of VLBWI.

The findings from this study are that the incidence of hypernatraemia in VLBWI admitted at CHBAH is very high at 33.8%. The majority of VLBWI who developed hypernatraemia were of gestational age less than 30 weeks. Only 30% of infants received antenatal steroids. All infants were started on a sodium containing fluid (Potassium-free Neonatalyte containing 33 mmol/L of sodium). The volume of fluids infants were started on at birth in ml/kg/day were almost similar for all weight categories and gestational ages. At time of diagnosis the severity of hypernatraemia was not related to gestational age, birth weight or to the amount of fluid or sodium that the infant was receiving. In the majority of patients the amount of fluid used to correct hypernatraemia was calculated based on a formula for free water-deficit. The method used to determine amount of fluids did not affect rate of

correction of hypernatraemia. The rate of correction of hypernatraemia was appropriate in the majority of cases, as only 8.4% had their sodium levels reducing by >1 mmol/hour. The environment under which infants were nursed did not affect the severity of hypernatraemia. Among the infants who had cranial ultrasounds done and results recorded, 15% had grade III IVH. The all-cause overall mortality rate in infants with hypernatraemia during the neonatal period was 22%, and the proportion of infants who died was greater in infants with smaller birth weight and younger gestational age.

Previous studies have shown that insensible water losses are higher the more premature an infant is, and therefore the higher the risk of hypernatraemia.[1,3,10] The severity of the hypernatraemia in this study was not affected by birth weight or gestational age. The lack of association between severity of hypernatraemia and birth weight in this study, could be explained by the fact that ELBWI were of higher gestational ages, or had more intensive management in order to limit IWL, such as the use of plastic covers in the unit for example.

The high incidence of hypernatraemia in this cohort could be related to the use of sodium containing fluids on admission. It is suggested that sodium intake should only start once there has been loss of approximately 6% of the birth weight.[8] Randomised trials have suggested that early administration of sodium increases the risk of hypernatraemia as well as the risks of respiratory morbidity by hampering the normal contraction of the extracellular fluid space.[8] There is a need for a prospective randomised control trial with infants being allocated to either a sodium free solution (10% dextrose) or Potassium-free Neonatalyte.

Once hypernatraemia was diagnosed, the majority of patients were managed with an increase in fluid volume with either a sodium-containing or sodium-free solution. The fact that the hypernatraemia resolved by adding free water alone, without restricting sodium intake support findings from previous studies that hypernatraemia in preterm or VLBWI is almost always due to increased insensible water losses.[6,10,11] Correcting hypernatraemia using sodium containing fluids may increase the sodium delivery more than the daily recommended amount and therefore delay resolution of hypernatraemia. Thus using a sodium-free solution like 5% dextrose water to correct water deficit that resulted in hypernatraemia appears to be appropriate. A formula that calculates water deficit to correct hypernatraemia has been suggested, and this formula was used in this study and appeared to be safe. [22]

Both phototherapy and radiant warmers have previously been reported to increase IWL. [6] It stands to reason that an infant nursed in a radiant warmer would have a higher risk for hypernatraemia and that it might take longer to resolve, however in this study hypernatraemia resolved faster in those nursed in a radiant warmer compared to those nursed in an incubator which was unexpected. The possible explanation for this is that infants nursed under radiant warmers are covered with plastic or a heat shield to limit heat loss and IWL as part of the unit or hospital protocol.

The number of infants who had cranial ultrasound done was small and this made it difficult to determine the incidence of IVH in infants with hypernatraemia. Reasons for the small number of ultrasounds include: a limited time available for the neonatologists to do the cranial sonars due to high volume of work and there is also the possibility that a cranial ultrasound was done on an infant but not documented in the file, especially those who are

found to be normal. Mortality in VLBWI is most likely multifactorial, therefore we looked at all-cause mortality rate as it is very difficult to assess mortality due to hypernatraemia on its own. The mortality rate in this cohort of babies was not much different from the overall mortality rate of 75% in VLBW infants in this neonatal unit. A common cause of mortality in VLBWI in this hospital is nosocomial sepsis, thus I would like to assume that even in this cohort, nosocomial sepsis was a common cause of death, as most of the deaths occurred at 7-28 days of life and yet the average time for resolution of hypernatraemia was 44 hours.

5.1 Study limitations

The major limitation for this study is that it is a retrospective study. As a retrospective record review, there was a risk of not being able to retrieve all the files or information in files being incomplete. The retrieval rate in this study however was more than one had expected at 83.5%, therefore it gave one an opportunity to get fairly good information regarding incidence. Availability of data relies on the accuracy and completeness of nurses and doctors notes, which is most likely the case for the low number of available ultrasound reports. This is often compromised in a retrospective study. The accuracy of volume and type of fluids in this study was verified by matching information from doctors orders and what the nurse administered. Major difficulties experienced was working out the rate of correction of hypernatraemia as one had to rely on times when blood specimens were received at the lab. The time that specimens were taken or when the results were acted upon were not always available.

6.0 CONCLUSION AND RECOMMENDATIONS

In conclusion, hypernatraemia is a common problem among VLBWI admitted in the neonatal division at CHBAH. Factors that might be contributing to high incidence of hypernatraemia could be related to use of sodium containing fluid from birth. The rate of correction of hypernatraemia was appropriate for most patients. Using a formula to correct free water deficit appears to be safe but a prospective study to confirm this is recommended as numbers in this study were small. Though correction of hypernatraemia appears to be appropriate in most patients, it is not clear as to what is the best fluid to use to correct hypernatraemia and how to calculate the volume. Therefore I recommend that prospective studies are conducted to assess the effect of using a sodium-free solution at birth on incidence of hypernatraemia, use of free-water deficit formula to correct hypernatraemia and lastly to accurately look at morbidities associated with hypernatraemia.

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APPENDIX A: DATA COLLECTION

Study Number:

1. **Maternal Details:**
   1.1. Age: _____ years
   1.2. Booked: ……..□ Yes □ No
   1.3. Place of Delivery: ……□ CHBH □ Clinic □ Other hospital □ Home
   1.4. Mode of delivery: ……..□ NVD □ C/S □ Breech □ Forceps/Vacuum
   1.5. Gravidity:
   1.6. Maternal illness: PIH DM Other:
   1.7. HIV: Pos Neg Unknown
   1.8. Antenatal steroids: ……..□ Yes □ No

2. **Infant Demographics:**
   2.1. Birth weight (grams):
   2.2. Gestational age:
   2.3. Apgar: 1 min 5min
   2.4. Gender: M F
   2.5. Time of birth:
   2.6. Date of birth:

3. **Fluid management at birth:**
   3.1. Name of fluid started at birth
      3.1.1. Oral: _____; Intravenous: _____
   3.2. Volume started at birth (Total) (mls/kg/day):
      3.2.1. Oral: _____ mls/kg/day, Intravenous: _____ mls/kg/day

4. **Fluid management at time of diagnosis of hypernatraemia**
   4.1. Name of fluids at time of dx of Hypernatraemia
      4.1.1. Oral: _____; Intravenous: _____
   4.2. Volume of fluid at time of dx of hypernatraemia (Total) (mls/kg/day):

4.2.1. Oral: _____ mls/kg/day, Intravenous: _____ mls/kg/day

5. <u>Fluid management in response to hypernatraemia</u>

5.1. Weight at time of response to hypernatraemia: _____ grams

5.2. Name of fluid ordered

5.2.1. Oral: _____; Intravenous: _____

5.3. Volume of fluid ordered (Total) mls/kg/day

5.3.1. Oral: _____ mls/kg/day, Intravenous: _____ mls/kg/day

5.4. Rate of increase of fluid (Total): _____ (mls/kg)

5.4.1. Rate of increase calculated based on formula (600xwt (kg)x (1-140/Curr.Na): ……. Yes No

5.4.2. If the answer is NO, state if it is more or less:.. More Less, & by what amount: ___mls/kg

5.5. Name of fluid increased

5.5.1. Oral: _____ mls/kg/day, Intravenous: _____ mls/kg/day

6. <u>Electrolyte results:</u>

	At diagnosis	**1st Result after Rx started**	**2nd Result after Rx started**	**3rd result after Rx started**
Na				
K				
Urea				
Creatinine				
Date U and E received				
Time U and E received at lab				
Type and vol fluid				
Rate of increase				

7. <u>Environmental factors:</u>

7.1. Nursed in/under: Incubator Radiant warmer

7.2. Phototherapy (1st 72 hours): ……..□ Yes □ No

7.3. Ventilation: CPAP CMV

8. <u>Outcomes (<28days old)</u>

8.1. IVH:

8.2. Survived/demised:

8.2.1. Died during ↑Na: ……..□ Yes □ No

8.2.2. If no, died within 7 days: ……..□ Yes □ No

8.2.3. Cranial sonar done: ……..□ Yes □ No

8.2.4. If yes, Grade IVH: 1 2 3 4

APPENDIX B: ETHICS CLEARANCE CERTIFICATE

M130652

R14/49 Dr Kim Barnard

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130652

NAME: (Principal Investigator)	Dr Kim Barnard
DEPARTMENT:	Paediatrics Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Hypernatraemia in very Low Birth Weight Infants Admitted at Chris Hani Baragwanath Academic Hospital: Incidence, Fluid Management and Factors Associated with its Severity
DATE CONSIDERED:	28/06/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Sithembiso Velaphi
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 28/06/2013

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

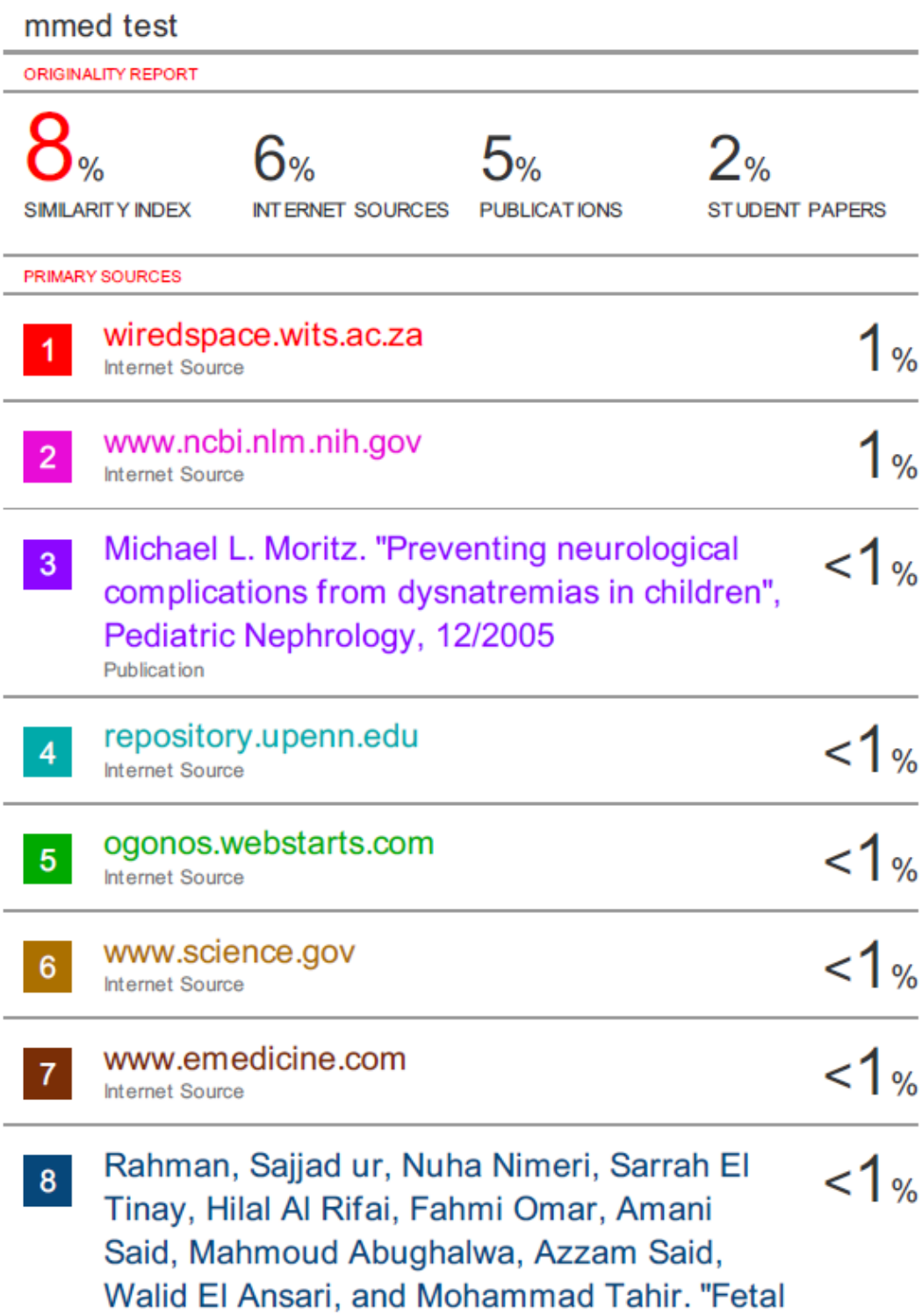
To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX C: "TURNITIN" REPORT



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