ADMISSION HYPOTHERMIA IN VERY LOW BIRTH WEIGHT NEWBORNS AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of a Master of Medicine (MMed) in Paediatrics.

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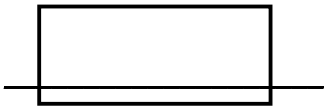
DECLARATION

I, Angidi Pillay MAUREE, declare that this research report is my own work. It is being submitted for the Degree of Master of Medicine at 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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ABSTRACT

Background: Hypothermia is associated with increased morbidity and mortality rates. Very low birth weight (VLBW) newborns are at an increased risk of hypothermia especially within the first few hours after delivery.

Objectives: To determine the prevalence, associated risk factors, and outcomes of admission hypothermia in VLBW newborns, at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a quaternary hospital in Johannesburg, South Africa.

Methods: This was a retrospective descriptive study of all VLBW newborns born over a seven year period (from 1st January 2013 to 31st December 2019) at CMJAH. Comparisons between hypothermic and normothermic newborns as well as between moderately-to-severely hypothermic and mildly hypothermic newborns were done. Multivariate binary logistic regression with 95% confidence interval and a p-value of < 0.05 was used to identify variables which had a significant association.

Results: Mean gestational age and birthweight of enrolled newborns was 28.9 ± 2.7 weeks and 1097 ± 250 g respectively. Prevalence of admission hypothermia was 61.5 % of which 54.3% was mild hypothermia, 43.9 % was moderate hypothermia and 1.8 % was severe hypothermia. VLBW newborns with hypothermia were more likely to have a birthweight < 1000 g [aOR 1.37 (1.12-1.68)] and less likely to be associated with early onset sepsis [aOR 0.51 (0.30-0.88)]. VLBW newborns with moderate to severe hypothermia were less likely than those with mild hypothermia to have received antenatal steroids [aOR 0.66 (0.48-0.89)]. There was no significant association of mortality in either VLBW newborns with hypothermia as compared to those with normothermia [aOR 0.95 (0.76-1.19), p value 0.67] or in VLBW newborns with moderate to severe hypothermia as compared to those with mild hypothermia [aOR 0.76 (0.46-1.26), p value 0.29].

Conclusions: Prevalence of admission hypothermia in VLBW newborns is high and reinforces the need for thermoprotective measures in this population.

(Word count: 294)

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I would also like to acknowledge the outstanding work done by the neonatal staff at Charlotte Maxeke Johannesburg Academic Hospital in terms of capturing data used in this study.

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PREFACE

This research report has been compiled in the "submissible format" in accordance with the University of the Witwatersrand Faculty of Health Sciences requirements for a research report. The abstract and manuscript has been prepared for submission to Frontiers in Pediatrics (see Appendix A for author guidelines) with the supervisors as co-authors. The approved research protocol (Appendix B), the plagiarism declaration certificate (Appendix C), the Human Research Ethics Committee approval certificate (Appendix D), and the Turnitin Report (Appendix E) have also been attached.

SUBMISSIBLE PAPER

Admission hypothermia in very low birth weight newborns at a quaternary hospital in South Africa

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ABSTRACT

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Conclusions: Prevalence of admission hypothermia in VLBW newborns is high and reinforces the need for thermoprotective measures in this population.

(Word count: 294)

1.0 INTRODUCTION

Hypothermia is associated with increased morbidity and mortality, especially in premature newborns.(1, 2) There is a 28% increase in mortality in very low birth weight (VLBW) newborns for every one degree decrease in temperature below 36.0 °C.(3) The World Health Organization (WHO) recognizes that thermal care in the neonatal period is of utmost importance, yet hypothermia continues to be globally under-reported, under-recognized and poorly managed.(4)

In 1997, the WHO came up with a standardized definition of normothermia as being a temperature in the range of 36.5 °C to 37.5 ºC.(5) Hypothermia < 36.5 °C was categorized into three subgroups based on the core temperature, prognosis and action required:

- Mild (cold stress): 36.0 °C – 36.4 °C. Cause for concern and need to warm the newborn and look for a cause.
- Moderate: 32.0 °C – 35.9 °C. Danger and need to immediately warm the newborn.
- Severe: < 32.0 °C. Grave outlook with requirement of urgent skilled care.

Globally, the incidence of admission hypothermia (AH) in VLBW newborns ranges between 31% and 78%.(3, 6, 7) The statistics from big cohorts in high income countries (HICs) are as follows: the Canadian Neonatal Network reported AH in 36% of preterm newborns < 33 weeks, the Effective Perinatal Intensive care in Europe showed AH in 54% of newborns < 32 weeks, 56% of VLBW newborns had AH in the California Perinatal Quality Care Collaborative and 77% of VLBW newborns from a Taiwanese study had AH.(2, 8-10) Studies from low- and middle-income countries (LMICs) reported AH prevalence in VLBW newborns of 46% in South Africa, 54% in Brazil and 65% in Malaysia.(11-13)

There are several physiological risk factors for AH in premature newborns. If exposed to the environment, premature newborns may experience a decrease in temperature postnatally at a rate of 0.5 – 1 °C per minute.(6) Mechanisms of heat loss include evaporation, conduction, convection and radiation.(6) A premature newborn possesses a relatively large body surface area (BSA) in relation to weight of up to four times that of an adult, decreased brown fat which is important for non-shivering thermogenesis and thinner skin with minimal stratum corneum.(1, 2, 8, 14) Prematurity has been shown to be the most important determinant of AH in VLBW newborns.(2) Other factors include an Apgar score < 7 at 5 minutes, newborns who had been resuscitated at birth or hypoglycemia at birth.(8, 12, 15-17) Studies in Brazil and Tanzania also showed that AH was more likely if a newborn was delivered outside of a hospital.(18, 19)

All of the above risk factors predispose to hypothermia which subsequently lead to increased risk of respiratory distress and need for surfactant administration.(2, 20) AH is also associated with complications such as sepsis, intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC) and bronchopulmonary dysplasia (BPD).(1, 2, 9) VLBW newborns with AH have longer hospital stays and higher mortality rates as compared to newborns with normothermia on admission.(2, 19, 20)

There is a paucity of data about the prevalence of AH using the WHO classification in VLBW newborns in LMICs, particularly in Africa. A study carried out in 2016 at Chris Hani Baragwanath Academic Hospital in South Africa reported a prevalence of 46 % of AH in VLBW

newborns and some of the associated factors relevant to AH in VLBW newborns in the South African context.(12)

This study aimed to review AH in VLBW newborns admitted to the neonatal unit at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a large referral hospital in South Africa – an upper middle-income country.

2.0 MATERIALS AND METHODS

Study design

This was a retrospective, descriptive study from 1st January 2013 to 31st December 2019. The study population included all VLBW newborns delivered at CMJAH as well as VLBW newborns who were transferred in within 24 hours post-delivery. Newborns with no record of initial admission temperature were excluded. Newborns with specific congenital abnormalities causing an increased risk of evaporative losses (e.g., myelomeningocele and abdominal wall defects) were also excluded.

Setting

CMJAH is a public quaternary hospital located in Johannesburg, South Africa. The neonatal unit consists of 104 beds, including levels 1 to 4 of neonatal care. These levels respectively refer to a well newborn nursery, a nursery offering special care, a neonatal intensive care unit and a regional neonatal intensive care unit.(21) The unit is attached to an obstetric unit within the hospital and also functions as a referral center for surrounding clinics and hospitals.

Database

This was a secondary analysis of an existing database. Neonatal records at CMJAH are kept in a computerized database for clinical audit and quality improvement purposes and managed using Research Electronic Data Capture (REDCap), which is hosted by the University of the Witwatersrand.(22, 23) Data was collected by clinicians using hospital records upon discharge, transfer or demise of the newborn from the neonatal unit. The data was checked and verified at several stages of collection before being entered into the database.

Variables

Compiled maternal variables included age, antenatal care attendance, multiple pregnancy, antenatal steroids, chorioamnionitis and Human Immunodeficiency Virus (HIV) status. Newborn characteristics included temperature on admission, sex, birthweight, gestational age, delivery mode, place of birth, Apgar score at 1, 5 and 10 minutes, highest delivery room resuscitation intervention, complications after delivery, duration of hospital stay and outcome on discharge.

The total sample was analyzed for baseline maternal and neonatal characteristics and then comparisons were drawn between the normothermia and the hypothermia subgroups. The hypothermia group was further divided into the mild hypothermia subgroup and a combined moderate-to-severe hypothermia subgroup for further analysis to be made.

Definitions

Definitions of complications of prematurity were based on those used in the Vermont Oxford Network (www.vtoxford.org).

- Sepsis was classified as positive if culture proven with early-onset within 72 hours of birth and late-onset after 72 hours postnatally.
- Necrotizing enterocolitis (NEC) was defined as NEC grade 2 or 3 according to the modified Bell's staging criteria.(24)
- Intraventricular hemorrhage (IVH) was defined as IVH grade 3 or 4 according to the Papile criteria.(25)
- Respiratory distress syndrome (RDS) was diagnosed in premature newborns requiring more than 40% FiO_2 after one hour of delivery with signs of respiratory distress and requiring surfactant use.
- Patent ductus arteriosus (PDA) was considered significant in newborns requiring medical and/or surgical intervention.
- Retinopathy of prematurity (ROP) was defined as Stage 2 or more.(26)
- Bronchopulmonary dysplasia (BPD) referred to newborns needing oxygen at 28 postnatal days.

Statistical analysis

Data was entered into a Microsoft Excel spreadsheet for data cleaning. The final dataset was then exported into the Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corporation, USA). Maternal and neonatal variables were assessed. Valid cases were analyzed and cases with missing data whereby no admission temperature was recorded were excluded. Categorical variables were described using frequencies and percentages. Continuous variables were described using means and standard deviations for normally distributed variables or medians and interquartile ranges for skewed variables. Categorical variables were compared using Chi- square tests and continuous variables with a normal distribution were compared using independent t-tests. Non-parametric tests such as the Mann- Whitney U test was used for skewed data. The level of significance was set at $p < 0.05$. Associations with hypothermia were determined using logistic regression. Variables that approached significance ($p < 0.1$) on univariate analysis were further explored with multivariate analysis.

Ethical approval and consent to participate

Anonymity of the data was ensured with the Microsoft Excel spreadsheet used for data cleaning containing a unique numerical identifier for each participant's name. The Human Research Ethics Committee of the University of the Witwatersrand granted ethics approval for the study (clearance certificate number: M200651). This was a retrospective study and the need for individual consent to participate was waived.

3.0 RESULTS

There was a total of 3 478 VLBW newborns eligible over the seven-year study period. We enrolled 2 678 (77.0%) newborns into the study after excluding 741 for no recorded temperature, 10 for congenital abnormalities associated with increased heat loss and 49 for presenting to CMJAH more than 24 hours post-delivery (Figure 1).

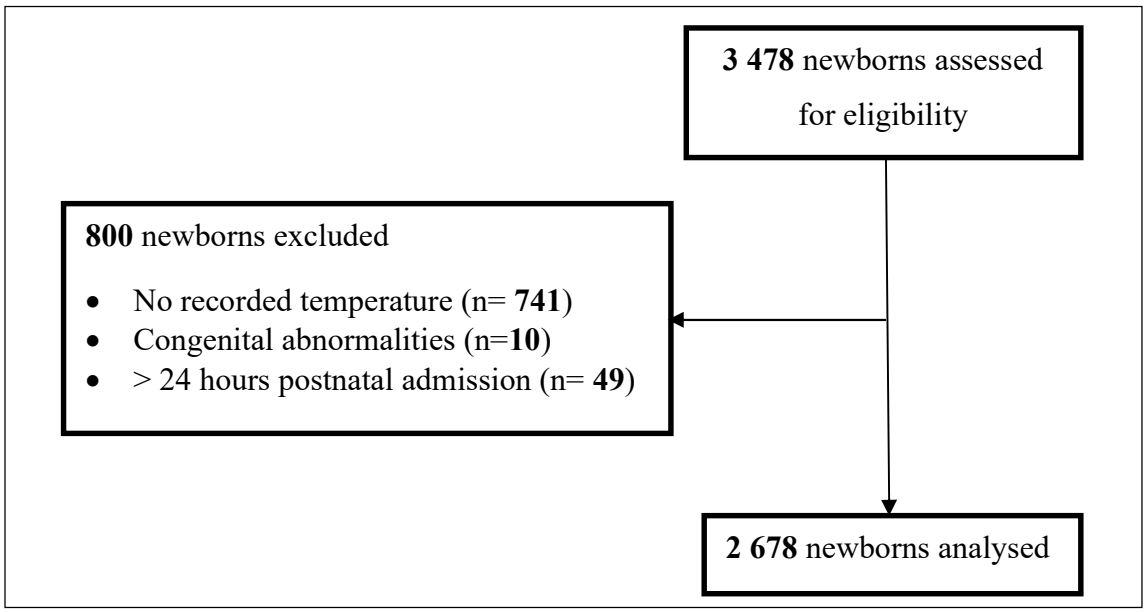

Figure 1: Study participants included in an analysis of very low birth weight newborns admitted to Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 – 31 December 2019.

Of the enrolled newborns, 61.5% (1 648/2 678) of them had hypothermia on admission, of whom 54.3% (895/1 648), 43.9% (723/1 648) and 1.8% (30/1 648) had mild, moderate and severe hypothermia respectively.

The mean (standard deviation (SD)) age of the mothers was 28 (9) years. Slightly more than three out of every four mothers (77.6%; 2 077/2 678) had received antenatal care and 46% (1 233/2 678) had been administered antenatal steroids. HIV positivity among this maternal cohort was 30.2% (785/2 678). Chorioamnionitis was diagnosed in 3% (81/2 678) of the mothers. There was 17.8 % (473/2 678) of mothers with multiparous pregnancies.

The mean birthweight and gestational age of the newborns was 1 097 (±250) grams and 28.9 (±2.7) weeks respectively. Most newborns were born at CMJAH (87.4%; 2 335/2 673), were female (53.1%; 1 422/2 678) and delivered by Caesarean Section (58.1%; 1 551/2 667). There were 3.3% (17/523) newborns with HIV.

Of the newborns who required resuscitation in the delivery room, the majority (85.1%; 2 279/2 678) necessitated oxygen (see Table 1 for a breakdown of the different types of resuscitation). After stabilization, the majority of the newborns (92.5%; 2 478/2 678) needed respiratory support at some point during their stay. A tenth of the newborns (9.9%; 265/2 678) developed metabolic acidosis (base excess < -16) while hypoglycemia (blood glucose< 2.6 mmol/L) was found in 14.3 % (384/2 678) of the newborns.

Nine out of every 10 (89.2%; 2 389/2 678) newborns developed RDS and seven out of 10 (70.8%; 1 895/2 678) newborns required surfactant administration. NEC was found in 7.7% (207/2 678) of newborns, 4.5% (35/780) of the newborns who had a documented ophthalmologic

screen were found to have ROP, approximately one out of 10 (257/2 678) newborns was diagnosed with a PDA and 17.6 % (270/ 1 531) of the newborns who had a cranial ultrasound performed were found to have IVH. There was a lower proportion of early onset sepsis (2.4%; 64/2 678) as compared to late onset sepsis (22.4%; 600/2 678).

The median (interquartile range) stay of the newborns was of 27 (34) days with a range of 0 to 234 days. About a quarter (24.5%; 655/2 678) of the newborns required oxygen at day 28 of life. The mortality rate was 30.4% (813/2 678) with less than one in twenty (4.4%; 36/813) of those dying doing so in the delivery room.

Table 1: Characteristics of the analyzed very low birth weight newborns admitted to Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013 – 31st December 2019.

Clinical characteristics of 2 678 enrolled newborns*	
Admission temperature (ºC) ψ (range)	36.0 (1.1) (26.4 – 38.8)
Temperature subgroup, n (%)	
Hypothermia	1 648 (61.5)
Normothermia	1 012 (37.8)
Hyperthermia	18 (0.7)
Hypothermia subgroup	
Severe hypothermia	30/1 648 (1.8)
Moderate hypothermia	723/1 648 (43.9)
Mild hypothermia	895/1 648 (54.3)
Delivery room, n (%)	
Apgar at 1 min < 7	1 197/2 498 (47.9)
Apgar at 5 min < 7	548/2 497 (21.9)
Apgar at 10 min < 7	227/2 331 (9.7)
Delivery room resuscitation, n (%)	
Oxygen	2 279 (85.1)
CPR	280 (10.5)
ETT	71 (2.7)
Respiratory support postnatally, n (%)	
Oxygen	2 478 (92.5)
CPAP	1 829 (68.3)
Ventilation	566 (21.1)

*: Denominator is 2678 unless otherwise specified. ψ: Expressed in mean (SD). CPAP: Continuous positive airway pressure, CPR: Cardiac compressions, ETT: Endotracheal intubation

<u>Comparing newborns in the hypothermia subgroup to newborns in the normothermia subgroup</u>

Out of all the newborns, there were 1648 (61.5%) newborns in the hypothermia subgroup as compared to 1012 (37.8%) newborns in the normothermia subgroup. The mean admission temperature was 35.5 (±1.1) ºC and 36.7 (±0.2) ºC in the hypothermia and normothermia subgroups respectively.

There was no significant difference in the maternal characteristics between the two subgroups. Newborns who were hypothermic were more likely to have a birthweight < 1000 g and to being delivered at < 30 weeks of gestation. This study showed that a newborn with hypothermia was found to have a lower birthweight (1080 g vs. 1126.8 g) and a lower gestation (28.8 weeks vs. 29.1 weeks) than a normothermic newborn. There was no significant difference between the two groups in sex, whether the pregnancy involved multiple gestation, in the mode of delivery or where the delivery occurred.

Newborns with hypothermia were more likely to have an Apgar score of < 7 at 5 minutes and there was no statistical difference in terms of Apgar score at 10 minutes. With regard to resuscitation in the delivery room, the study showed that there was an association between hypothermia and use of cardiac compressions. There was no significant difference in terms of the usage of different modalities of respiratory support postnatally between the two subgroups.

This study showed that a hypothermic newborn was more likely to develop metabolic acidosis. There was no marked difference in terms of other morbidities namely RDS, NEC, ROP, IVH, PDA, sepsis, or BPD.

A VLBW newborn with hypothermia was more likely to die as opposed to one with normothermia. There was no marked difference between the two groups with regard to length of hospital stay: hypothermic newborns had a median (IQR) stay of 27 (36) days as opposed to normothermic newborns who stayed for 28 (30) days [OR 1.00 (0.999-1.005), p 0.16].

Table 2: Categorical variables comparing the characteristics between very low birth weight newborns admitted with hypothermia to those with normothermia at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013- 31 December 2019.

Characteristics	Hypothermia (N=1648) ψ	Normothermia (N = 1012) *	Unadjusted OR	95% CI	p value
Maternal characteristics, n (%)					
Antenatal care	1 266 (76.8)	797 (78.8)	0.89	0.74-1.08	0.25
Antenatal steroids	743 (45.1)	486 (48)	0.89	0.76-1.04	0.14
Chorioamnionitis	47 (2.9)	33 (3.3)	0.87	0.55-1.37	0.55
Newborn characteristics, n (%)					
ELBW	609 (37)	797 (29.2)	1.42	1.20-1.67	<0.001
Gestation < 30 weeks	1033 (62.7)	580 (57.4)	1.05	1.02-1.08	0.007
Male gender	749 (45.5)	496 (49.1)	0.87	0.74-1.01	0.075
Multiple gestation	298 (18.1)	175 (17.3)	1.06	0.86-1.30	0.61
Born via Caesarean section	938 (57.1)	603/1 005 (60)	0.89	0.76-1.04	0.14
Inborn	1 435 (87.3)	886 (87.6)	0.97	0.76-1.23	0.79
Delivery room and respiratory support, n (%)					
Apgar score < 7 (5 min)	361/1 521 (23.7)	181/960 (18.9)	1.34	1.10-1.64	0.004
Apgar score < 7 (10 min)	148/1 428 (10.4)	76/888 (8.6)	1.24	0.92-1.65	0.15
Delivery room resuscitation	1417 (86.0)	866 (85.6)	1.03	0.83-1.29	0.77

Oxygen	1410 (85.6)	856 (84.6)	1.08	0.87-1.34	0.49
ETT	40 (2.4)	31 (3.1)	0.79	0.50-1.27	0.32
Cardiac compressions	189 (11.5)	90 (8.9)	1.33	1.02-1.73	0.035
Postnatal Respiratory Support	1 563 (94.8)	962 (95.1)	0.96	0.67-1.37	0.80
Oxygen	1 529 (92.8)	934 (92.3)	1.07	0.80-1.44	0.64
CPAP	1 124 (68.2)	693 (68.5)	0.99	0.83-1.17	0.88
Ventilation	332 (20.1)	228 (22.5)	0.87	0.72-1.05	0.14
Complications, n (%)					
Hypoglycemia	240 (14.6)	141 (13.9)	1.05	0.84-1.32	0.65
RDS	1 484 (90)	888 (87.7)	1.26	0.99-1.62	0.064
Surfactant use	1170 (71.0)	713 (70.5)	1.03	0.86-1.22	0.77
Metabolic acidosis	180 (10.9)	83 (8.2)	1.37	1.05-1.80	0.022
NEC	124 (7.5)	83 (8.2)	0.91	0.68-1.22	0.53
ROP	23/465 (4.9)	12/307 (3.9)	1.28	0.63-2.61	0.24
IVH	161/757 (17.5)	106/602 (17.6)	1.00	0.76-1.30	0.97
PDA	155 (9.4)	100 (9.9)	0.95	0.73-1.23	0.69
EOS	32 (1.9)	31 (3.1)	0.63	0.38-1.03	0.065
LOS	357 (21.7)	236 (23.3)	0.91	0.75-1.10	0.32
Outcome, n (%)					
Day 28 oxygen	388 (23.5)	259 (25.6)	0.90	0.75-1.07	0.23
Mortality in delivery room	25/527 (4.7)	11/280 (3.9)	1.22	0.59-2.51	0.59
Mortality	527 (32)	280 (27.7)	1.23	1.04-1.46	0.019

ψ Denominator for variables is 1648 unless otherwise specified, * Denominator for variables is 1012 unless otherwise specified. Analysis by Chi Squared testing.

CI: Confidence Interval, CPAP: Continuous Positive Airway Pressure, ELBW: Extremely Low Birth Weight, EOS: Early Onset Sepsis, ETT: Endotracheal intubation, IVH: Intraventricular Hemorrhage, LOS: Late Onset Sepsis, NEC: Necrotizing Enterocolitis, OR: Odds Ratio, PDA: Patent Ductus Arteriosus, RDS: Respiratory Distress Syndrome, ROP: Retinopathy of Prematurity

Variables with p value of less than 0.1 were entered into a multivariate binary logistic regression model.

Out of the categorical variables of ELBW vs birthweight of 1000-1500g, gestation < 30 weeks vs gestation ≥ 30 weeks and the continuous variables of birthweight and gestation, the categorical variable of ELBW vs birthweight of 1000-1500 g was chosen as it was the most significant one.

A binomial logistic regression was then performed to ascertain the effects of being born with ELBW, male sex, Apgar at 5 minutes being < 7, having CPR in the delivery room, presence of metabolic acidosis, RDS, early onset sepsis and death on the likelihood that the newborns will have hypothermia. Linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell (1962) procedure. A Bonferroni correction was applied using all in the model resulting in statistical significance being accepted when $p< 0.003$. The logistic regression model was statistically significant, χ^2 (8) = 34.898, $p<0.001$. The model explained 1.9% (Nagelkerke R^2) of the variance in admission temperature and correctly classified 61.4 % of cases. Sensitivity was 98.9%, specificity was 2%, positive predictive value was 61.5% and negative predictive value was 54.3%. Of the predictor variables, only birthweight and early onset sepsis were independently associated with AH. A newborn with hypothermia was 1.37 (95 % CI: 1.12-1.68) more likely than one with normothermia to be born with a birthweight

< 1000 g. Early onset sepsis was less likely in those with hypothermia as compared to those with normothermia (aOR 0.51, 95% CI: 0.30-0.88).

Table 3: Logistic regression for significant variables after having compared the characteristics between very low birth weight newborns admitted with hypothermia to those with normothermia at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013- 31 December 2019.

Variables	Adjusted OR	95% CI	p value
ELBW	1.37	1.12-1.68	**0.002**
Male gender	0.86	0.73-1.01	0.07
Apgar at 5 min <7	1.16	0.91-1.49	0.24
CPR	1.14	0.84-1.55	0.41
Metabolic acidosis	1.07	0.79-1.46	0.66
RDS	1.21	0.94-1.57	0.15
EOS	0.51	0.30-0.88	**0.02**
Death	0.95	0.76-1.19	0.67

CI: Confidence Interval, CPR: Cardio-Pulmonary Resuscitation, ELBW: Extreme Low Birth Weight, EOS: Early Onset Sepsis, OR: Odds ratio, RDS: Respiratory Distress Syndrome

Comparing newborns in the moderate to severe hypothermia subgroup to newborns in the mild hypothermia subgroup.

The mean (SD) admission temperature in the moderately to severely hypothermic and the mildly hypothermic subgroups was 34.8 (1.3) º C and 36.2 (0.2) º C respectively. Out of the newborns with hypothermia, 45.7% (753/1 648) were in the moderate to severe hypothermia subgroup and 54.3 % (895/1 648) were in the mild hypothermia subgroup. Mothers to newborns with moderate to severe hypothermia were less likely to have received antenatal care or antenatal steroids as compared to mothers with newborns with mild hypothermia.

The newborns with moderate to severe hypothermia as opposed to those with mild hypothermia were also found to be more likely associated with having been born with an extremely low birth weight and to have a gestation of less than thirty weeks. Newborns with moderate to severe hypothermia were less likely to have been delivered by caesarean section or born at CMJAH as opposed to a newborn with mild hypothermia.

Newborns in the moderate to severe hypothermia subgroup had significantly lower Apgar scores at five and ten minutes than those with mild hypothermia. Those found to have moderate to severe hypothermia as compared to those with mild hypothermia were found to most likely require CPR and intubation in the delivery room and more likely to develop metabolic acidosis and IVH. Having late onset sepsis was less likely in those with moderate to severe hypothermia as compared to those with mild hypothermia.

VLBW newborns with moderate to severe hypothermia were more likely to have a shorter median (IQR) length of hospital stay than those with mild hypothermia [25(39) days versus 27 (32) days, OR 1.005 (1.002- 1.009), p 0.006]. A VLBW newborn with moderate to severe

hypothermia as compared to one with mild hypothermia was more likely to die and this was also significant in the delivery room.

Table 4: Categorical variables comparing the characteristics between very low birth weight newborns admitted with moderate to severe hypothermia to those with mild hypothermia at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013- 31 December 2019.

Characteristics	Moderate to Severe hypothermia (N=753) ᵠ	Mild hypothermia (N= 895) *	Unadjusted OR	95% CI	p value
Maternal characteristics, n (%)					
Antenatal care	543 (72.1)	723 (80.8)	0.62	0.49-0.77	<0.001
Antenatal steroids	282 (37.5)	461 (51.5)	0.56	0.46-0.69	<0.001
Chorioamnionitis	21 (2.8)	26 (2.9)	0.96	0.54-1.72	0.89
Newborn characteristics, n (%)					
ELBW	313 (41.6)	296 (33.1)	1.44	1.18-1.76	<0.001
Gestation< 30 weeks	497/744 (66.8)	527/890 (59.2)	1.39	1.13-1.70	0.002
Male gender	328 (43.6)	421 (47.1)	0.87	0.71-1.05	0.15
Multiple gestation	133 (17.7)	165 (18.4)	0.95	0.74-1.22	0.69
Caesarean section	378 (50.3)	560 (62.7)	0.60	0.50-0.73	<0.001
Inborn	615 (81.8)	820 (91.9)	0.39	0.29-0.53	<0.001
Delivery room and postnatal respiratory support, n (%)					
Apgar score< 7 (5 min)	191/666 (28.7)	170/855 (19.9)	1.62	1.28-2.06	<0.001
Apgar score<7 (10 min)	87/618 (14.1)	61/810 (7.5)	2.01	1.42-2.84	<0.001
Delivery room resuscitation	644 (85.5)	773 (86.4)	0.93	0.71-1.23	0.62
Oxygen	641 (85.1)	769 (85.9)	0.94	0.71-1.24	0.65
Cardiac compressions	107 (14.2)	82 (9.2)	1.64	1.21-2.23	0.001
Intubation	27 (3.6)	13 (1.5)	2.52	1.29-4.93	0.005
Respiratory support postnatally	713 (94.7)	850 (95)	0.94	0.61-1.46	0.80
Oxygen	696 (92.4)	833 (93.1)	0.91	0.63-1.32	0.62
CPAP	512 (68)	612 (68.4)	0.98	0.80-1.21	0.87
Ventilation	163 (21.6)	169 (18.9)	1.19	0.93-1.51	0.16
Complications, n (%)					
Hypoglycemia	113 (15)	127 (14.2)	1.07	0.82-1.41	0.64
RDS	679 (90.2)	805 (89.9)	1.03	0.74-1.42	0.88
Surfactant use	533 (70.8)	637 (71.2)	0.98	0.79-1.22	0.86
Metabolic acidosis	105 (13.9)	75 (8.4)	1.77	1.30-2.42	<0.001
NEC	48 (6.4)	76 (8.5)	0.73	0.50-1.07	0.11
ROP	10/203 (4.9)	13/262 (5.0)	0.99	0.43-2.31	0.99

IVH	85/411 (20.7)	76/507 (15)	1.48	1.05-2.08	0.024
PDA	73 (9.7)	82 (9.2)	1.06	0.76-1.48	0.71
EOS	16 (2.1)	16 (1.8)	1.19	0.59-2.40	0.62
LOS	146 (19.4)	211 (23.6)	0.78	0.62-0.99	0.04
Outcome, n (%)					
Day 28 oxygen	167 (22.2)	221 (24.7)	0.87	0.69-1.09	0.23
Mortality	287 (38.1)	240 (26.8)	1.68	1.36-2.07	<0.001
Mortality in delivery room	20/287 (7)	5/240 (2.1)	3.52	1.30-9.53	0.009

ψ Denominator for variables is 753 unless otherwise specified, * Denominator for variables is 895 unless otherwise specified. Analysis by Chi Squared testing

CI: Confidence Interval, CPAP: Continuous Positive Airway Pressure, ELBW: Extreme Low Birth Weight, EOS: Early Onset Sepsis, IVH: Intraventricular Hemorrhage, LOS: Late Onset Sepsis, NEC: Necrotizing Enterocolitis, OR: Odds Ratio, PDA: Patent Ductus Arteriosus, RDS: Respiratory Distress Syndrome, ROP: Retinopathy of Prematurity

Variables with p value of less than 0.1 were entered into a multivariate binomial logistic regression model. Out of the categorical variables of ELBW vs birthweight of 1000- 1500g and gestation < 30 weeks vs gestation ≥ 30 weeks, the first variable was chosen as it was the most significant one.

A binomial logistic regression was performed to ascertain the likelihood of moderate to severe hypothermia as compared to mild hypothermia after taking into account if the newborn had antenatal care, antenatal steroids, having been born with ELBW, having been delivered via caesarean section, having been delivered at CMJAH, having had a recorded Apgar score of less than 7 at 5 and 10 minutes respectively, having had cardiac compressions and been intubated in the delivery room, having developed metabolic acidosis or intraventricular hemorrhage, having developed late onset sepsis, length of stay and dying. Linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box- Tidwell (1962) procedure. A Bonferroni correction was applied using all in the model resulting in statistical significance being accepted when p< 0.002. The logistic regression model was statistically significant, $\chi 2$ (14) = 25.35, p< 0.021. The model explained 4.3% (Nagelkerke R^2) of the variance in admission temperature and correctly classified 59.6 % of cases. Sensitivity was 23.7%, specificity was 85.9%, positive predictive value was 55.2% and negative predictive value was 60.6%. Of the 14 predictor variables, only antenatal steroids were found to be statistically significant. Those newborns with moderate or severe hypothermia were found to have a lower association with antenatal steroids than those with mild hypothermia (OR 0.66).

Table 5: Logistic regression for significant variables after having compared the characteristics between very low birth weight newborns admitted with moderate to severe hypothermia to those with mild hypothermia at Charlotte Maxeke Johannesburg Academic Hospital, 1 January 2013- 31 December 2019.

Variables	Adjusted OR	95% CI	p value
Antenatal care	1.25	0.83-1.87	0.29
Antenatal steroids	**0.66**	**0.48-0.89**	**0.007**
ELBW	1.00	0.71-1.40	0.99
Born via caesarean section	0.75	0.64-1.04	0.09
Inborn	1.09	0.55-2.18	0.80

Apgar at 5 min <7	1.19	0.75-1.87	0.46
Apgar at 10 min <7	1.14	0.58-2.24	0.71
CPR	0.94	0.5501.62	0.83
ETT use	1.47	0.47-4.57	0.51
Metabolic acidosis	1.64	0.95-2.84	0.08
IVH	1.37	0.92-2.04	0.12
LOS	0.92	0.65-1.31	0.64
Length of stay	1.00	0.99-1.01	0.66
Death	0.76	0.46-1.26	0.29

CI: Confidence Interval, CPR: Cardio-Pulmonary Resuscitation, ELBW: Extreme Low Birth Weight, ETT: Endotracheal intubation, IVH: Intraventricular Hemorrhage, LOS: Late Onset Sepsis, OR: Odds ratio

4.0 DISCUSSION

Key findings

There is limited information on AH in VLBW newborns especially in Sub Saharan Africa. Our study, carried out in a large academic quaternary hospital in Johannesburg, South Africa, shows that approximately three out of every five (61.5%) VLBW newborns were hypothermic on admission to the neonatal unit postdelivery. This is a higher prevalence than some of the reported rates in HICs but comparable to the studies done in LMICs.(8-11, 13, 16) There was a very small prevalence of VLBW newborns who were hyperthermic (0.7%).

Out of all the newborns with hypothermia, slightly less than half of them had moderate to severe hypothermia (45.7%). This is a particularly high percentage which shows that there could be more implementation of appropriate temperature regulation measures. Looking at the overall characteristics of the VLBW newborns, it could be appreciated that almost nine out of ten were born at CMJAH. It is worth noting that the study showed that almost 1 in 3 VLBW newborns passed away.

Comparing VLBW newborns with hypothermia to VLBW newborns with normothermia

On univariate analysis, VLBW newborns with AH as compared to those with normothermia were found to more likely be of ELBW and to be of gestational age < 30 weeks. Adjusting for other independent variables still resulted in a newborn with birthweight < 1000 g being 1.37 times more likely to experience AH as opposed to a normal temperature. This was in accordance with other studies where a lower birthweight and gestational age were associated with admission hypothermia. (1, 2) Contributing reasons would entail all the physiological factors that predispose newborns to lose heat the more preterm they are.

AH was not associated with the newborn's gender, the mode of delivery and whether the child was born at CMJAH or transferred in within 24 hours postnatally. One similar study in South Africa had shown that AH was associated with vaginal delivery while another study from the USA had shown the association with being delivered by caesarean section. (10, 12) This study also did not show that AH was associated more with outborn patients coming to the referral center as evidenced by studies in Tanzania and Brazil and this might be due to our high proportion of newborns who are inborn in both subgroups. (18, 19)

This current study showed that maternal age, antenatal care or steroids and presence of chorioamnionitis did not have any association with AH.

This study showed that a newborn with AH was more likely to have an Apgar score of less than 7 at 5 minutes as opposed to someone with normothermia as supported by a study by Miller et al. (10). The interaction between Apgar score and temperature might be that hypothermia at birth leads to increased need for resuscitation and therefore a lower Apgar score at 5 minutes or that conversely resuscitation with a low Apgar score leads to uncovering the newborn and therefore hypothermia on the first recorded temperature.

Studies done in Africa by Demissie et al. (Ethiopia) or Ng'eny et al. (South Africa) have shown that there is an association between the need for resuscitation at birth and subsequent AH. Our study showed that a newborn who received cardiac compressions was associated with developing AH and this might be due to the fact that increased exposure for the compressions predispose to the cold.

AH has also been associated with metabolic acidosis whereby hypothermia causes peripheral vasoconstriction with increased oxygen demand leading to anaerobic metabolism and metabolic acidosis. (12, 14) This was found in our study but not supported when doing the logistic regression model.

A previous study had reported that there is a 28% increase in mortality in VLBW newborns for every one degree decrease in temperature below 36.0 °C. (3) The univariate analysis in our study showed that a VLBW newborn with hypothermia was more likely to die as compared to one with normothermia but this was not confirmed on multivariate analysis. A potential explanation could be that the detrimental consequence of mortality could have been prevented by the sick newborn having access to High Care or Intensive Care Unit and having adequate management of the consequences brought by hypothermia.

Apart from the association between birthweight and admission hypothermia, the only other variable which had a significant association when doing the logistic regression model was early onset sepsis. Our study highlighted that newborns with hypothermia were less likely to develop early onset sepsis than those with normothermia. A potential explanation could be that there is closer supervision of newborns diagnosed with hypothermia once they get admitted to the neonatal unit.

Comparing VLBW newborns with moderate to severe hypothermia to VLBW newborns with mild hypothermia

We found that the odds of developing moderate to severe hypothermia were significantly lower by using antenatal steroids and this is supported by Miller et al. (10) This is probably attributed to the fact that a mother who had received steroids antenatally was more likely to have a newborn with better lung function; leading to less risk of respiratory distress at birth and less need for resuscitation. Another explanation could be that a mother presenting early enough to a healthcare facility and receiving steroids also predisposes the newborn to be in a better environment; preventing factors leading to more severe hypothermia.

This study also showed that a VLBW newborn with moderate to severe hypothermia as compared to mild hypothermia was less likely to have a mother who attended a clinic antenatally

but this was not statistically significant when the multivariate logistic regression was carried out. This still highlights the importance of the mother making an early appointment during pregnancy and to follow up regularly.

Our study showed that the lower the birthweight and gestational age, there was an association with moderate to severe hypothermia as opposed to normothermia. This was however not supported by the multivariate logistic regression. Newborns born by vaginal delivery were more likely to have moderate or severe hypothermia and this could be due to the sub-optimal temperature in the delivery room which is an open room as compared to the better controlled temperature in the operating theatres. There is also a dedicated member from the neonatal team at the delivery of a VLBW newborn in theatre as compared to at a vaginal delivery; allowing for implementation of thermoprotective measures more promptly in the first case. Newborns who were referred to CMJAH from other units were more likely to experience moderate to severe hypothermia than mild hypothermia and this is most likely linked with suboptimal incubator temperature or inadequate wrapping during transfer. Being delivered outborn was a risk factor as suggested by studies in other LMICs such as Brazil, Ethiopia and Tanzania. (16, 18, 19)

The more severe the hypothermia, this was associated with an Apgar score of less than seven at five minutes and at ten minutes and an increased association with requiring chest compressions or needing to be endotracheally intubated. Resuscitation usually means that the newborn has to be fully exposed to gain intravenous access and for compressions to be done and this leads to the newborn losing even more heat on top of already being predisposed as compared to a term newborn.

In terms of complications, being moderately to severely hypothermic was associated with metabolic acidosis and IVH. The development of metabolic acidosis was supported by other studies and could be explained by the increased oxygen demand leading to anaerobic metabolism in a newborn with a lower temperature. The etiology of IVH is multifactorial and the association with a newborn with moderate to severe hypothermia could be due to that newborn requiring resuscitation.

This study surprisingly demonstrated that there was a lower association of late onset sepsis in the VLBW newborn with moderate to severe hypothermia. This might be linked to the higher association of death in that group during the hospital stay. Out of all the deaths, it was found that a newborn with moderate to severe hypothermia was 3.5 times more likely to die in the delivery room than a newborn with mild hypothermia.

The only variable which was found to be statistically significant after taking into account the independent variables, was the use of antenatal steroids which was found to decrease the severity of the degree of hypothermia in a VLBW newborn. This further reinforces the administration of any dose of steroids for the eligible mothers.

5.0 STUDY LIMITATIONS

The retrospective nature of this study meant that establishing a temporal relationship between some variables was difficult and there was additionally incomplete or missing data. A fifth of newborns did not have their initial temperature recorded and this large proportion could alter the

overall results. The inherent risk of bias brought by the retrospective nature of the study might have been minimized by the large sample size.

Furthermore, some information such as the exact time of when the first temperature or first glucose measurement was recorded postnatally was not routinely collected. We also do not know that the first temperature value was actually entered into the database in the event of several temperature recordings within the first hour. The room temperature to which each of the VLBW newborns was exposed on delivery would also be a variable that would be worth recording and should be at a minimum of 25°C as recommended by the WHO and definitely not always achieved. There was a high prevalence of maternal HIV results and this could be attributed to the negative results not being recorded in the notes. A mother living with HIV was also more likely to know her HIV status, be on treatment and report it and therefore have her result recorded. The high number of unknown HIV results might also be explained by information captured at the time of delivery not being subsequently captured.

The protocol of measuring temperature is usually done on the skin in the unit and it is possible that the temperature measured on the skin is lower than measured rectally.

There might have been inter-observer variability in the diagnosis of IVH and Ballard scoring. We can only comment on associations in this study.

6.0 CONCLUSIONS AND RECOMMENDATIONS

This study showed a high prevalence of admission hypothermia in VLBW newborns. AH was associated with a lower birthweight but was inversely associated with early onset sepsis. This study also found that the use of antenatal steroids was less associated with moderate to severe hypothermia as compared to mild hypothermia. Our study further showed that there was no increase in mortality in firstly VLBW newborns with hypothermia as compared to those with normothermia and secondly in VLBW newborns with moderate to severe hypothermia as compared to those with mild hypothermia.

This highlights the importance of ensuring that all thermoprotective factors are implemented as soon as a newborn is delivered while following the guidelines by the Resuscitation Council of Southern Africa.(27) A VLBW newborn being wrapped by plastic after delivery is part of the current practice at CMJAH. This might not however have always been promptly practiced by the first attending health care practitioner who is most often a medical intern still getting used to the delivery of newborns.

There should also be a general consensus with all studies looking at admission hypothermia in newborns to abide by the WHO criteria of subcategorization of hypothermia.

There should be ongoing quality improvement programs aimed at educating healthcare practitioners about rapidly recognizing and implementing measures to prevent or address AH especially in VLBW newborns. Further studies could be carried out to focus on comparing data before and after any interventions aimed at addressing hypothermia and also look at associations with short- term and long- term outcomes.

Further studies could focus on the difference in AH between daytime and nighttime and also between different seasons. One could also look at the relation between number of doses of antenatal steroids and its effect on hypothermia (moderate to severe versus mild).

Contribution to the field statement

Hypothermia is associated with increased morbidity and mortality. Due to several physiological risk factors, very low birth weight (VLBW) newborns are at increased risk of hypothermia especially within the first few hours after birth. Incidence of admission hypothermia (AH) in VLBW newborns ranges between 31% and 78%. The World Health Organisation recognises that hypothermia is still however under-reported, under-recognised and poorly managed. This is especially relevant to low-and-middle income settings such as South Africa (SA). This study was designed to investigate the prevalence, associated risk factors and outcomes of AH in VLBW newborns in a large quaternary hospital in SA. We further investigated what impact different severities of hypothermia had on VLBW newborns at birth. This study confirmed that the more preterm a newborn was, the more likely he was to be hypothermic at birth. Early onset sepsis was also associated with normothermia as compared to hypothermia. We also found out that the use of antenatal steroids was associated with a lower severity of hypothermia in VLBW newborns. Mortality was not observed to be associated with hypothermia. With the high prevalence of AH in VLBW newborns, we emphasise the importance of implementing thermoprotective factors from birth.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions: APM conceptualized and designed the study, collected data, carried out data analysis, drafted the initial manuscript; DEB conceptualized and designed the study, supervised the study and reviewed and revised the manuscript, and approved the final manuscript; and RS supervised the study, reviewed and revised the manuscript.

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ABBREVIATIONS

AH	Admission Hypothermia
BMV	Bag Mask Ventilation
BPD	Bronchopulmonary Dysplasia
BSA	Body Surface Area
CI	Confidence Interval
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CPR	Cardio-Pulmonary Resuscitation
ELBW	Extremely Low Birth Weight
EOS	Early Onset Sepsis
HICs	High Income Countries
LBW	Low Birth Weight
LMICs	Low- and Middle-Income Countries
LOS	Late Onset Sepsis
NEC	Necrotizing Enterocolitis
PDA	Patent Ductus Arteriosus
RDS	Respiratory Distress Syndrome
ROP	Retinopathy of Prematurity
TU	Transitional Unit
VLBW	Very Low Birth Weight
WHO	World Health Organization

KEY TERMS

Admission temperature: First temperature obtained from a newborn in theatre or on admission to the transitional unit

Severe hypothermia (WHO) Axillary temperature < 32.0ºC

Moderate hypothermia (WHO): Axillary temperature 32.0- 35.9 ºC

Mild hypothermia (WHO): Axillary temperature 36.0- 36.4 ºC

Hypothermia (WHO): Axillary temperature < 36.5ºC

Normothermia (WHO): Axillary temperature 36.5- 37.5 º C

Hyperthermia (WHO): Axillary temperature > 37.5 ºC

Inborn: Newborn delivered at CMJAH

Outborn: Newborn delivered outside of CMJAH

Prematurity: Less than 37 weeks completed gestational age

Extremely Low Birth Weight (ELBW): Newborn weighing < 1000 g

Very Low Birth Weight (VLBW): Newborn weighing < 1500 g

Low Birth Weight (LBW): Newborn weighing < 2500 g

Bronchopulmonary Dysplasia (BPD): Oxygen requirement by newborn at 28 postnatal days

Intraventricular Hemorrhage (IVH): As per Papille classification, Grade 3 and 4 were considered significant in this study

Necrotizing Enterocolitis (NEC): Modified Bell's stage 2 or 3

Patent Ductus Arteriosus (PDA): Significant PDA necessitating medical and/ or surgical intervention

Respiratory Distress Syndrome (RDS): Premature newborn requiring > 40% FiO_2 after 1 hour of delivery with signs of respiratory distress and requiring surfactant use

Retinopathy of Prematurity (ROP): Refers to ROP requiring intervention (any stage ROP with plus disease in Zone I, Stage 3 ROP without plus disease in Zone I, Stage 2 or 3 ROP with plus disease in Zone II)

Sepsis: Sepsis proven on blood culture; excluding likely skin commensals e.g. Coagulase Negative Staphylococcus (CNS)

Early onset sepsis: Sepsis occurring within the first 72 hours after birth

Late onset sepsis: Sepsis occurring later than 72 hours after birth

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APPENDIX A: GUIDELINES FOR AUTHORS

Author guidelines

General standards

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Frontiers requires authors to select the appropriate article type for their manuscript and to comply with the article type descriptions defined in the journal's 'Article types' page, which can be seen from the 'For authors' menu on every Frontiers journal page. Please pay close attention to the word count limits.

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Frontiers encourages the authors to closely follow the article word count lengths given in the 'Article types' page of the journals. The manuscript length includes only the main body of the text, footnotes, and all citations within it, and excludes the abstract, section titles, figure and table captions, funding statement, acknowledgments, and references in the bibliography. Please indicate the number of words and the number of figures and tables included in your manuscript on the first page.

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There are a few simple ways to maximize your article's discoverability. Follow the steps below to improve the search results of your article:

- include a few of your article's keywords in the title of the article
- do not use long article titles
- pick 5-8 keywords using a mix of generic and more specific terms on the article subject(s)
- use the maximum amount of keywords in the first two sentences of the abstract
- use some of the keywords in level 1 headings.

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The title should be concise, omitting terms that are implicit and, where possible, be a statement of the main result or conclusion presented in the manuscript. Abbreviations should be avoided within the title.

Witty or creative titles are welcome, but only if relevant and within measure. Consider if a title meant to be thought-provoking might be misinterpreted as offensive or alarming. In extreme cases, the editorial office may veto a title and propose an alternative. Authors should avoid:

- titles that are a mere question without giving the answer
- unambitious titles, for example starting with 'Towards,' 'A description of,' 'A characterization of' or 'Preliminary study on'
- vague titles, for example starting with 'Role of', 'Link between', or 'Effect of' that do not specify the role, link, or effect

- including terms that are out of place, for example the taxonomic affiliation apart from species name.

For Corrigenda, General Commentaries, and Editorials, the title of your manuscript should have the following format:

- 'Corrigendum: Title of Original Article'
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The running title should be a maximum of five words in length.

Authors and affiliations

All names are listed together and separated by commas. Provide exact and correct author names as these will be indexed in official archives. Affiliations should be keyed to the author's name with superscript numbers and be listed as follows:

- Laboratory, Institute, Department, Organization, City, State abbreviation (only for United States, Canada, and Australia), and Country (without detailed address information such as city zip codes or street names).

Example: Max Maximus1 1 Department of Excellence, International University of Science, New York, NY, United States.

Correspondence

The corresponding author(s) should be marked with an asterisk in the author list. Provide the exact contact email address of the corresponding author(s) in a separate section. Example: Max Maximus* maximus@iuscience.edu If any authors wish to include a change of address, list the present address(es) below the correspondence details using a unique superscript symbol keyed to the author(s) in the author list.

Equal contributions

The authors who have contributed equally should be marked with a symbol (†) in the author list of the doc/latex and pdf files of the manuscript uploaded at submission.

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Abstract

As a primary goal, the abstract should render the general significance and conceptual advance of the work clearly accessible to a broad readership. In the abstract, minimize the use of abbreviations and do not cite references, figures or tables.

Keywords

All article types require a minimum of five and a maximum of eight keywords.

Text

The entire document should be single-spaced and must contain page and line numbers in order to facilitate the review process. The manuscript should be written using either Word or LaTeX. See above for templates.

Nomenclature

The use of abbreviations should be kept to a minimum. Non-standard abbreviations should be avoided unless they appear at least four times, and must be defined upon first use in the main text. Consider also giving a list of non-standard abbreviations at the end, immediately before the acknowledgments.

We encourage the use of Standard International Units in all manuscripts.

Sections

The manuscript is organized by headings and subheadings. The section headings should be those appropriate for your field and the research itself. You may insert up to 5 heading levels into your manuscript (i.e.,: 3.2.2.1.2 Heading Title).

For Original Research articles, it is recommended to organize your manuscript in the following sections or their equivalents for your field.

Introduction Succinct, with no subheadings.

Materials and methods This section may be divided by subheadings and should contain sufficient detail so that when read in conjunction with cited references, all procedures can be repeated. For experiments reporting results on animal or human subject research, an ethics approval statement should be included in this section (for further information, see the 'Bioethics' section of our polices and publication ethics.)

Results This section may be divided by subheadings. Footnotes should not be used and must be transferred to the main text.

Discussion This section may be divided by subheadings. Discussions should cover the key findings of the study: discuss any prior research related to the subject to place the novelty of the discovery in the appropriate context, discuss the potential shortcomings and limitations on their interpretations, discuss their integration into the current understanding of the problem and how this advances the current views, speculate on the future direction of the research, and freely postulate theories that could be tested in the future.

For further information, please check the descriptions defined in the journal's 'Article types' page, in the 'For authors' menu on every journal page.

Acknowledgments

This is a short text to acknowledge the contributions of specific colleagues, institutions, or agencies that aided the efforts of the authors.

Contribution to the field statement

When you submit your manuscript, you will be required to briefly summarize in 200 words your manuscript's contribution to, and position in, the existing literature in your field. This should be written avoiding any technical language or non-standard acronyms. The aim should be to convey the meaning

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Example statement on: Markram K and Markram H (2010) The Intense World Theory – a unifying theory of the neurobiology of autism. Front. Hum. Neurosci. 4:224. doi: 10.3389/fnhum.2010.00224

Autism spectrum disorders are a group of neurodevelopmental disorders that affect up to 1 in 100 individuals. People with autism display an array of symptoms encompassing emotional processing, sociability, perception and memory, and present as uniquely as the individual. No theory has suggested a single underlying neuropathology to account for these diverse symptoms. The Intense World Theory, proposed here, describes a unifying pathology producing the wide spectrum of manifestations observed in autists. This theory focuses on the neocortex, fundamental for higher cognitive functions, and the limbic system, key for processing emotions and social signals. Drawing on discoveries in animal models and neuroimaging studies in individuals with autism, we propose how a combination of genetics, toxin exposure and/or environmental stress could produce hyper-reactivity and hyper-plasticity in the microcircuits involved with perception, attention, memory and emotionality. These hyper-functioning circuits will eventually come to dominate their neighbors, leading to hyper-sensitivity to incoming stimuli, over-specialization in tasks and a hyper-preference syndrome. We make the case that this theory of enhanced brain function in autism explains many of the varied past results and resolves conflicting findings and views and makes some testable experimental predictions.

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The text should be legible and of high quality. The smallest visible text should be no less than eight points in height when viewed at actual size.

Solid lines should not be broken up. Any lines in the graphic should be no smaller than two points wide.

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Ensure sufficient contrast between text and its background People who have low visual acuity or color blindness could find it difficult to read text with low contrast background color. Try using colors that provide maximum contrast.

WC3 recommends the following contrast ratio levels:

- Level AA, contrast ratio of at least 4.5:1
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You can verify the contrast ratio of your palette with these online ratio checkers:

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- Color Safe

Avoid using red or green indicators More than 99% of color-blind people have a red-green color vision deficiency.

Avoid using only color to communicate information Elements with complex information like charts and graphs can be hard to read when only color is used to distinguish the data. Try to use other visual aspects to communicate information, such as shape, labels, and size. Incorporating patterns into the shape fills also make differences clearer; for an example please see below:

Supplementary material

Data that are not of primary importance to the text, or which cannot be included in the article because they are too large or the current format does not permit it (such as videos, raw data traces, PowerPoint presentations, etc.), can be uploaded as supplementary material during the submission procedure and will be displayed along with the published article. All supplementary files are deposited to Figshare for permanent storage and receive a DOI.

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- The reference list should only include articles that are published or accepted
- Unpublished data, submitted manuscripts, or personal communications should be cited within the text only, for article types that allow such inclusions
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Many Frontiers journals use the numbered referencing system; to find the correct reference style and resources for the journal you are submitting to, please visit our help center.

Reference examples are found below, for more examples of citing other documents and general questions regarding the Vancouver reference style, please refer to Citing Medicine.

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Reference examples

Article in a print journal Sondheimer N, Lindquist S. Rnq1: an epigenetic modifier of protein function in yeast. Mol Cell (2000) 5:163-72.

Article in an online journal Tahimic CGT, Wang Y, Bikle DD. Anabolic effects of IGF-1 signaling on the skeleton. Front Endocrinol (2013) 4:6. doi: 10.3389/fendo.2013.00006

Article or chapter in a book Sorenson PW, Caprio JC. "Chemoreception". In: Evans DH, editor. The Physiology of Fishes. Boca Raton, FL: CRC Press (1998). p. 375-405.

Book Cowan WM, Jessell TM, Zipursky SL. Molecular and Cellular Approaches to Neural Development. New York: Oxford University Press (1997). 345 p.

Abstract Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, editor. Genetic Programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3–5; Kinsdale, Ireland. Berlin: Springer (2002). p. 182–91.

Website World Health Organization. E. coli (2018). https://www.who.int/news-room/fact-sheets/detail/e-coli [Accessed March 15, 2018].

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Data Perdiguero P, Venturas M, Cervera MT, Gil L, Collada C. Data from: Massive sequencing of Ulms minor's transcriptome provides new molecular tools for a genus under the constant threat of Dutch elm disease. Dryad Digital Repository. (2015) http://dx.doi.org/10.5061/dryad.ps837

Theses and dissertations

Smith, J. (2008) Post-structuralist discourse relative to phenomological pursuits in the deconstructivist arena. [dissertation/master’s thesis]. [Chicago (IL)]: University of Chicago

Preprint Smith, J. Title of the document. Preprint repository name [Preprint] (2008). Available at: https://persistent-url (Accessed March 15, 2018).

APPENDIX B: RESEARCH PROTOCOL

ADMISSION HYPOTHERMIA IN VERY LOW BIRTH WEIGHT NEWBORNS AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of a Master of Medicine (MMed) in Paediatrics.

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May 2020

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ABBREVIATIONS

AH	Admission Hypothermia
BMV	Bag Mask Ventilation
BPD	Bronchopulmonary Dysplasia
BSA	Body Surface Area
CI	Confidence Interval
CHBAH	Chris Hani Baragwanath Academic Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CPR	Cardio- Pulmonary Resuscitation
ELBW	Extremely Low Birth Weight
EOS	Early Onset Sepsis ≤ 72 hours
HICs	High Income Countries
LBW	Low Birth Weight
LMICs	Low and Middle Income Countries
LOS	Late Onset Sepsis > 72 hours
NEC	Necrotising Enterocolitis
PDA	Patent Ductus Arteriosus
RDS	Respiratory Distress Syndrome
ROP	Retinopathy of Prematurity
TU	Transitional Unit
VLBW	Very Low Birth Weight
WHO	World Health Organisation

KEY TERMS

Admission temperature: First temperature obtained from a newborn in theatre or on admission to the transitional unit

Severe hypothermia (WHO) Axillary temperature < 32.0°C

Moderate hypothermia (WHO): Axillary temperature 32.0- 35.9 °C

Mild hypothermia (WHO): Axillary temperature 36.0- 36.4 °C

Hypothermia (WHO): Axillary temperature < 36.5°C

Normothermia (WHO): Axillary temperature 36.5- 37.5 ° C

Hyperthermia (WHO): Axillary temperature > 37.5 °C

Inborn: Newborn delivered at CMJAH

Outborn: Newborn delivered outside of CMJAH

Prematurity: Less than 37 weeks completed gestational age

Extremely Low Birth Weight (ELBW): Newborn weighing < 1000 g

Very Low Birth Weight (VLBW): Newborn weighing < 1500 g

Low Birth Weight (LBW): Newborn weighing < 2500 g

Bronchopulmonary Dysplasia (BPD): Oxygen requirement by newborn at 28 postnatal days

Intraventricular Haemorrhage (IVH): As per Papille classification, Grade 3 and 4 were considered significant in this study

Necrotising Enterocolitis (NEC): Modified Bell's stage 2 or 3

Patent Ductus Arteriosus (PDA): Significant PDA necessitating medical and/ or surgical intervention

Respiratory Distress Syndrome (RDS): Premature newborn requiring > 40% FiO_2 after 1 hour of delivery with signs of respiratory distress and requiring surfactant use

Retinopathy of Prematurity (ROP): Refers to ROP requiring intervention (any stage ROP with plus disease in Zone I, Stage 3 ROP without plus disease in Zone I, Stage 2 or 3 ROP with plus disease in Zone II)

Sepsis: Sepsis proven on blood culture; excluding likely skin commensals e.g Coagulase Negative Staphylococcus (CNS)

"If a definition of life were required, it must be most clearly on that capacity by which the animal preserves its proper heat under the various degrees of temperature of the medium in which it lives… a few degrees of increase or diminution of the heat of the system, produces disease and death."

James Currie. 1808

1. INTRODUCTION

1.1 Background

Hypothermia is associated with increased morbidity and mortality; especially in premature newborns. [1, 2] Admission hypothermia (AH), which is the first recorded temperature, is inversely proportional to mortality. With every drop in temperature by one degree celsius below 36 °C in newborns weighing 401-1499 g, there is a 28% increase in mortality and an 11% increase in late onset sepsis. [2, 3, 6] There are fewer rates of adverse neonatal outcomes in preterm newborns less than 33 weeks gestational age if the first recorded temperature is between 36.5 and 37.2 °C. [9] This is in line with the World Health Organization (WHO) recommendations on decreasing heat loss in newborns. [5, 9] The WHO recognises that thermal care in the neonatal period is of utmost importance; however hypothermia continues to be globally under reported, under recognized and poorly managed. [4]

The main contributors to worldwide neonatal deaths consist of infections, preterm delivery complications, congenital anomalies and intrapartum related hypoxic events. Infections constitute a third of the global burden and this is usually associated with a rise in temperature. [28]Hypothermia is unfortunately often overlooked and not considered to be as an equal contributor to morbidity and mortality. [28, 29]

1.2 Definition

There was no consistent definition of the upper and lower limits of normothermia in the newborn until it was standardized by the WHO in 1997. [5] The WHO defined neonatal normothermia as a temperature in the range of 36.5° C to 37.5 °C and hyperthermia as > 37.5°C. [5] Hypothermia < 36.5 °C was categorized into three subgroups based on the core temperature, prognosis and action required:

- Mild (cold stress): 36.0°C- 36.4°C. Cause for concern and need to warm the newborn and look for a cause.
- Moderate: 32.0-35.9°C. Danger; requiring immediate warming of the newborn.
- Severe: < 32.0°C. Grave outlook; requiring urgent skilled care.

Sub-categorization of hypothermia differing from the WHO classification, as well as different sites of temperature measurement (axillary, rectal); have led to a wide range in the reported global prevalence of AH. [8] Adopting the WHO standardized case definitions universally, such as the WHO classification of neonatal thermoregulation, is vital to gain a true reflection of hypothermia. An appropriate action plan can then be adopted worldwide, be it in High Income Countries (HICs) or in Low and Middle-Income Countries (LMICs).

1.3 Risk factors for admission hypothermia

Humans are homeotherms meaning that they must independently produce heat to maintain normothermia within a narrow range, unlike poikilotherms whose body temperature can change significantly with the external environment. [28] Fetal temperature is approximately 0.5º C higher than maternal temperature in utero, resulting from a combination of fetal endogenous heat production which is twice that of an adult, and of surrounding core maternal temperature. [4, 14]

Newborn infants, especially if premature and exposed, generally experience a drop in temperature postnatally via evaporation, conduction, convection, and radiation at a rate of 0.5 to 1 º C per minute. [6] Evaporation is the major source of heat loss in the first two weeks with heat always being transferred from the newborn to the environment; initially this is due to the evaporation of the amniotic fluid within the first thirty minutes postnatally. [14] Heat loss may persist if the ambient air humidity is low, if the newborn's skin is wet or if the newborn is wrapped in wet blankets. [14] Heat transfer by conduction occurs when heat from the newborn is lost by contact with a cooler object such as a table, weighing scale or cold mattress with which the newborn is in contact. [14] Convection arises due to the temperature gradient between the newborn and air (on average 37 and 27 º C respectively). [14] Radiant heat loss occurs when heat is lost to cooler objects not in direct contact with the newborn such as walls and windows. [4, 14, 20, 30] It has been shown that a naked newborn exposed to a room temperature of 23 º C at birth will suffer the same rate of heat loss as a naked adult at 0 º C. [4]

Preterm newborns have a relatively large body surface area (BSA) in relation to weight (term newborns have a 2.7 times greater BSA and premature newborns up to 4 times greater BSA per weight compared to an adult). [8] Being preterm also implies decreased subcutaneous fat and thinner skin with minimal stratum corneum (2-3 cell layers in preterm newborns versus 10-20 cell layers in term newborns), which ordinarily serves as a resistance barrier to water diffusion. Being a preterm newborn also implies a thinner layer of keratin, which further exacerbates water loss (newborns < 30 weeks of gestation lose 129 g/kg of water versus 7 g/kg of water in term newborns with each gram of water equating to 580 calories of heat lost). [1, 6, 8, 14] Compared to term newborns, preterm newborns also have less brown fat, which is important for non- shivering thermogenesis as part of the adaptive response to thermal stress. [2, 14] If there is significant heat loss, this results in decreased energy available to keep up with the resting metabolic rate of 40 kcal/ kg/day at birth. [4] The metabolic rate varies as follows: it can be increased by colostrum ingestion, increased activity, cold exposure, being awake and infection or reduced by illness especially hypoxia and asphyxia, starvation and deep sleep. [4]

Birth weight has been shown to be the most important determinant of AH in very low birth weight (VLBW) newborns. [2, 11, 15, 17, 18] A study done in Ethiopia showed that low birth weight (LBW) newborns were 3.7 times more likely than newborns with normal weight to get AH and there were similar results from a study in Pakistan. [15] In a Nepalese study, the risk for hypothermia was as follows: 1.49- fold times higher for those between 2000-2499 g, 4.32- fold times higher for those between 1500-1999 g and 17.3- fold times higher for those in the VLBW subgroup compared to newborns weighing ≥ 2500 g at birth. [31] In a study done at Chris Hari Baragwanath Academic Hospital

(CHBAH), hypothermia in the VLBW group was more likely if birthweight was < 1000 g [adjusted Odds ratio of 2.28]. [12]

An Apgar score <7 at one minute has been shown to be significantly associated with moderate hypothermia in newborns. [2, 10, 15, 17] Hypothermia was also more commonly associated with a five minute Apgar score < 7 compared to ≥ 7 and this could be attributed to increased resuscitative efforts or secondary to an inherent illness; of which hypothermia may be a marker or the result. [15] Demissie et al showed that VLBW newborns who had been resuscitated at birth were 3.6 times more likely to be hypothermic when compared to newborns who did not require resuscitation. [16] This was consistent with the study by Ng'eny et al at CHBAH. [12] One of the postulated reasons could be that poor resuscitative efforts result in lack of oxygen in brown adipose tissue required for heat production. [16]

Birth by caesarean section has been shown to potentially contribute to AH in VLBW newborns as operating theatres are often kept at cooler temperatures. [10] This differed in the study by Ng'eny et al where AH in VLBW newborns was more prevalent following a normal vaginal delivery than a caesarean section. [12] Use of positive pressure ventilation (PPV) with unheated gas in the delivery room has been associated with a 1.4- fold times higher odds of AH in preterm newborns <33 weeks gestational age. [7] Hypoglycaemia during resuscitation is another significant contributor to AH and vice versa. [8]

Maternal age <18 years, multiparity or lower socio-economic background have all been associated with a greater prevalence of AH. [8, 17] Maternal hypothermia at delivery, especially if moderate or severe, has been associated with a 1.45- fold the risk of AH in newborns. [28]

Silveira at al showed that newborns who had travelled more than 50 km from one health care unit to another were at an increased risk of AH and this was supported by another study in Tanzania. [18, 19] Furthermore, cultural practices may contribute to AH. In some communities, massage and oil application is done immediately postnatally to clean the newborn of 'dirty skin' and this has been shown to thin the protective barrier and lead to further heat loss. [8] In Ghana, newborns receive a bath postnatally so that they achieve better sleep and have a better body odour while newborns in Bangladesh may be exposed outdoors and newborns in India might be bathed up to three times a day. [4]

1.4 Prevalence

1.4.1 Globally

Approximately 16% (slightly more than 20 million newborns) of all live births worldwide are born with LBW; and 96% are found in LMICs. [4] Approximatively a fifth of them die annually during the neonatal period with a daily mortality rate during that interval being thirty times higher than during the rest of infancy. [8] This also represents two thirds of all deaths in the first year of life and 40% of overall under-5 deaths. [8] During the first 28 days of life, 75% of mortality occurs in the first week of life with 25-45% occurring in the 24 hours postnatally. [8] LMICs are where 99% of all the neonatal deaths arise, with the commonest causes being infections, preterm delivery complications, congenital anomalies and intrapartum related hypoxic events. [29]

AH has already been established as a major contributor to mortality: prevalence of hypothermia in hospital based studies ranged from 8% to 85 % and from 11% to 92% in community based studies. [8] Neonates are vulnerable even in hot tropical environments. [20] The prevalence of AH as a direct or indirect cause of death might be under-represented; given that only 2.5% of all neonatal deaths come from areas with reliable registries. [8, 14]

Looking at VLBW newborns specifically, the incidence of hypothermia was found to range from 31% and 78%. [6] It is reported that there is almost half (47%) of newborns ≤ 28 weeks who have AH, with 51% in those between 23-24 gestational weeks of age. [3, 7]

1.4.2 High Income Countries

A Canadian Neonatal Network report on 9833 preterm newborns < 33 weeks showed that despite adequate bundles of thermal care initiative, there were 36 % of newborns who developed AH, with an associated significant increase in morbidity and mortality compared to normothermic newborns. [9] Results from the Effective Perinatal Intensive Care in Europe (EPICE) study done across centres in 11 countries showed that 54% of 5697 preterm newborns < 32 weeks had AH. [8] In the United States, there has been a drop in the proportion of VLBW newborns with AH from 47 % in 2002 to 26 % in 2006. [9] In a cohort of 8782 VLBW newborns admitted in the California Perinatal Quality Care Collaborative, 56% were hypothermic. [10] The prevalence of AH in VLBW newborns over a 4 year period in Taiwan was of 77%. [2]

1.4.3 Low and Middle Income Countries

The incidence of hypothermia has been looked at both in out born and in hospital newborns in LMICs. In South Asia, community based studies conducted in Pakistan, Bangladesh, Bhutan and mostly in India and Nepal showed the prevalence of AH among newborns to range between 11% and 92%, and in hospital the prevalence ranged from 8% to 85%. [32] Studies done in Iran and Brazil showed that a third of all newborns became hypothermic immediately after birth. [17, 18]The prevalence of AH in VLBW newborns in 32 Malaysian Neonatal Intensive Care Unit (NICU) centres was 65% (40% mild, 59% moderate and 1% severe). [11]

In African hospital- based studies, AH across all newborns ranged between 22% and 85%; with 22% in Tanzania, 44% in Zambia, 83% in Uganda and 85% in Zimbabwe. [8] The prevalence of AH in LBW newborns in Ethiopia was 73 % and among VLBW newborns in Nigeria, it was 93 %. [8, 16, 33] A study carried out at CHBAH in 2016 showed the prevalence of AH among VLBW newborns to be 46 % which was similar to the AH prevalence of 54 % obtained by the Brazilian Neonatal Network study which evaluated over 4000 VLBW newborns across twenty centres. [12, 13]

1.5 Consequences of hypothermia

Hypothermia predisposes to increased severity of respiratory distress via increase in oxygen consumption and the resulting anaerobic metabolism leads to pulmonary vasoconstriction and decreased surfactant release. [2]. Of those who initially had a temperature of < 35.8 ºC, 35% of 65 premature newborns did not survive to discharge regardless of whether they were given oxygen or continuous

positive airway pressure (CPAP). This showed the importance of aggressively addressing AH before providing CPAP to a newborn, especially in LMICs. [20] There is also an increased need to administer surfactant in those with AH as evidenced by a study in Taiwan where surfactant use was indicated in 58% of newborns with moderate hypothermia versus in 39 % newborns without hypothermia(p= 0.006). [20]

AH is associated with hypoglycaemia, arrhythmia, bleeding, sepsis and intraventricular haemorrhage (IVH). [1, 2] IVH is found in 20-25% of VLBW newborns, and particularly in those with moderate hypothermia. [10, 34, 35] The lower the first recorded temperature, the higher the risk of neurological injury, severe retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD) and late onset infection. [2, 9]

AH was associated with a five times higher risk of having mild to moderate hypothermia over the next 3 hours, as well as having a lower temperature for longer periods as compared to normothermic newborns; which in itself perpetuates the above complications. [1] VLBW newborns with AH have longer hospital stays compared to newborns with normothermia on admission. [19] There is a 30-fold increase in mortality in preterm infants with AH versus those with normothermia; compared to only a 2-fold increase in term newborns. [2, 20] The mortality rate in VLBW newborns with AH in Taiwan was 13.2 % (18.5% in the moderate hypothermia group versus 5.1% in the mild hypothermia group). [2]

A Californian study showed that 26 % of VLBW newborns had an increased risk of mortality because of moderate/severe hypothermia following birth and this fared better compared to the case fatality rate in LMICs. [10, 33] In a large Brazilian study, isolated hypothermia predicted 42% of all the deaths and a South African study done at CHBAH showed that AH was associated with a 5- fold increase in mortality during the first week of life in VLBW newborns if hypothermic on admission. [12, 13]

1.6 Prevention

It can be a challenge to keep VLBW newborns warm but it is essential to ensure this, particularly in those <28 weeks gestation or weighing < 1000 g. [2] Thermoprotective factors are currently implemented as bundles of care and are part of essential newborn care. The Resuscitation Council of Southern Africa has a step by step running timeline on the left hand side of its newborn resuscitation algorithm to remind the resuscitator to maintain normothermia. [27]

Standard thermal care that needs to be undertaken with emphasis in VLBW newborns; including the Extremely Low Birth Weight (ELBW) group are: [2, 4, 6, 7, 10, 14, 35]

- Ensuring warm delivery, recovery and postpartum rooms at 24- 25° C according to the WHO.
- Keeping the room humidity at least at 50%.
- Drying the newborn if VLBW and if ELBW; covering with plastic/ polyethylene and putting a cap on.
- Removing any wet blankets or clothes.
- Using servo controlled radiant warmers and transwarmer mattresses.
- Using preheated incubators for transport.
- Starting skin to skin contact with the mother and immediate breastfeeding if possible.

- Using heated and humidified air postnatally and during transport.

1.7 Rationale for current study

There is paucity of data about the prevalence of AH using the WHO classification in VLBW newborns in LMICs; particularly in Africa. A study carried out in 2016 at CHBAH reported the prevalence and some of the associated factors relevant to AH in VLBW newborns in the South African context. This study aims to supplement existing local literature by gathering and exploring more information about this topic over a longer study period and with a bigger cohort of patients at a quarternary hospital in Johannesburg.

2. STUDY AIM AND OBJECTIVES

2.1 Study aim

To determine the prevalence of, associated risk factors and outcomes in VLBW newborns with admission hypothermia at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

2.2 Objectives

a) To determine the prevalence of AH in VLBW newborns and to sub-categorise hypothermia using the WHO definition.
b) To describe factors associated with AH in VLBW newborns.
c) To determine the case fatality rate associated with AH; stratified by birthweight, gestational age and postnatal age of death.

3. METHODOLOGY

3.1 Study design

A retrospective, descriptive study of newborns weighing < 1500 g presenting to the neonatal unit at CMJAH, Johannesburg, South Africa between 1st January 2013 and 31st December 2019. This is a secondary analysis of an existing database.

3.2 Study population

CMJAH is an accredited central quaternary level hospital located in Parktown in Johannesburg, South Africa; with 104 beds in the neonatal unit. CMJAH receives referrals from surrounding clinics such as Alexandra and Hillbrow and also delivers services to patients from across Gauteng and the neighbouring provinces.

High risk obstetric patients are followed up during their pregnancies at CMJAH leading to a setting which specializes in the management of high- risk deliveries. There are approximately 9000 deliveries annually with 2000 newborn admissions, about 450 of which are VLBW newborns. All newborns born in theatre, the sick newborns born by a normal vaginal delivery and transfers from other clinics or hospitals are all assessed in the Transitional Unit (TU) and a decision is subsequently made on the need for admission.

The newborn might then be discharged to the mother or admitted to the Low care ward, High care ward or to the NICU. These areas are staffed by dedicated nurses, paediatric registrars/ residents and consultant paediatricians.

3.3 Inclusion criteria

All preterm neonates with a birthweight < 1500 g admitted to the neonatal TU between 1st January 2013 and 31st December 2019 will be included in the study. These will consist of inborn and out born neonates presenting < 24 hours postnatally.

3.4 Exclusion criteria

Those newborns with major congenital abnormalities (because of increased risk of evaporative losses) including congenital brain malformations, malformations resulting in an open lesion (eg myelomeningocoele and abdominal wall defects), those dead or moribund on arrival, as well as those without record of admission skin temperature will be excluded.

3.5 Study method, data collection and Handling

Neonatal doctors collect demographic and clinical information on all newborns upon discharge, transfer or demise from the neonatal unit at CMJAH, for the purpose of quality improvement and clinical audit. The relevant data is verified several times before being entered into a computer database. The data is managed using Research Electronic Data Capture (REDCap) hosted by the University of the Witwatersrand. [23] This REDCap database will be used to identify all newborns meeting inclusion and exclusion criteria. Each newborn will be allocated a study number and the relevant data for each participant, as per the data collection sheet, will be extracted from the database and entered into an Excel spreadsheet.

The axillary temperature is routinely measured to the nearest tenth of a degree celsius on admission of the newborn to TU. If the temperature was measured several times within the first hour after admission, the first temperature value would have been entered into the database. There is no actual record of when exactly the temperature is recorded postnatally within the first hour of life.

3.6 Statistical Analysis

No sample size has been calculated, and the convenience sample will be determined by the number of patients in the registry who correspond to the entry criteria for the study. There are approximately 450 VLBW newborns admitted to CMJAH annually and we expect to include about 3000 cases over a 7-year period before applying the exclusion criteria.

The basic demographics and clinical characteristics of eligible cases will be reported using means and standard deviations for normally distributed continuous variables while medians with range and interquartile ranges will be used for non- normally distributed continuous variables. Categorical variables will be reported using frequencies and percentages. Tables and graphs will be used to represent the results.

Data management and statistical analyses will be performed using Statistical Package for the Social Sciences (SPSS) Version 26.

The total sample will be divided into those VLBW newborns with normothermia and those with AH. In initial analyses, characteristics of the normothermic and AH sub- groups will be compared. The Chi square test or Fischer's exact test will be used for categorical variables while the Student t test or Mann-Whitney U- test will be used for continuous variables; depending on the data distribution. If there are more than 15 patients in each hypothermia sub- group, comparisons will also be done between the different groups of hypothermic newborns. P values <0.05 will be considered statistically significant. Only valid cases for each variable will be included in the analysis.

Variables with P values< 0.1 will be entered into a binary logistic regression model to determine the independent relationships between maternal and infant characteristics/ outcomes and admission temperature.

4. LIMITATIONS

Given that it is a retrospective study, the available information will depend on:

- Proper recording of results at the time of admission of the patients
- Accurate capture of information on the REDCap database

Bias might occur in the following situations:

- Timing of when first temperature is recorded.
- Inter- observer variability in the diagnosis of IVH.
- Ambient temperature might not have been the same daily.
- If the Ballard score was not done properly, there would have been improper classification of gestational age.

5 ETHICAL CONSIDERATIONS

5.1 Risks

There are no anticipated risks for the participants given that it is a retrospective study.

5.2 Confidentiality

Personal patient details will not be included in the study. Given that it is a retrospective study with the information already pre- existing in a database, there will be no need to obtain consent from the enrolled patients and their caregivers.

5.3 Review board approval

Approval for the protocol prior to data collection will be obtained at the University of Witwatersrand from

→ The Human Research Ethics Committee.

5.4 Permissions

Permission will be obtained from the database gatekeeper for use of the REDCap system. Permissions will also be required from the Head of Department of Paediatrics at CMJAH as well as from the Chief Executive Officer of CMJAH.

6 FUNDING

The principal investigator will cover all costs associated with carrying out the research. Costs include stationery, photocopying and printing. The estimated allocated amount will be less than R 5,000.

7. TIMELINE

	2020								
Milestones	**Apr**	**May**	**Jun**	**Jul**	**Aug**	**Sep**	**Oct**	**Nov**	**Dec**
Literature review	■								
Protocol preparation	■	■							
Protocol assessment			■						
Ethics approval			■	■					
Data collection					■				
Data analysis					■	■			
Writing up research report						■	■		
Supervisor review								■	■
Writing up publication									■

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Unique Numerical Identifier	**N…….**				
Admission temperature _____^{o} C	Severe hypothermia (< 32^{o}C) (1)	Moderate hypothermia (32-35.9 ^{o}C) (2)	Mild hypothermia (36.0-36.4^{o}C) (3)	Normothermia (36.5-37.5^{o}C) (4)	Hyperthermia (> 37.5^{o}C) (5)

Date of Birth:_____	**Date of admission:_____**	**Temp within 1st hour:** Yes (1) No (2)

MATERNAL CHARACTERISTICS

Maternal age (years)				
Antenatal care received	Yes(1)	No(2)	Unknown(3)	
Use of antenatal steroids (any dose of corticosteroid given prior to delivery)	Yes (1)	No(2)	Unknown(3)	
Clinical chorioamnionitis (mother with fever, uterine tenderness and/or foul amniotic fluid)	Yes(1)	No(2)	Unknown(3)	
HIV status	Yes(1)	No(2)	Unknown(3)	

NEWBORN CHARACTERISTICS

Gender	Male(1)	Female(2)	Ambiguous(3)	
Multiplicity	No(1)	Yes (2)-number:		
Birthweight (grams)				
Gestational age (weeks)				
HIV status	Positive (1)	Exposed and negative(2)		Negative (3)
Mode of delivery	NVD(1)	C/S(2)	Breech (3)	Unknown (4)
Inborn/ Outborn	Inborn (1)	Outborn(2)	Unknown (3)	

DELIVERY ROOM VARIABLES

Apgar score at 1 min	Value:___	<7 (1)	≥7 (2)		
Apgar score at 5 min	Value:___	<7 (1)	≥7 (2)		
Apgar score at 10 min	Value:___	<7 (1)	≥7 (2)		
Highest Delivery room resuscitation intervention	Oxygen – neopuff/ BMV (1)	CPR (2)	Adrenaline (3)	Intubation (4)	
First Glucose reading (mmol/L)	≤ 2.6 (1)	> 2.6 (2)			
Metabolic acidosis (BE<-16)	Yes (1)	No (2)			

COMPLICATIONS

Respiratory distress	Yes (1)	No (2)					
Surfactant use	Yes (1)	No (2)					
NEC (modified Bell's stage 2/3)	Yes (1)	No (2)	NEC surgery Yes (1) No (2)				
ROP needing intervention	Yes (1)	No (2)					
IVH (Grade 3 / 4)	Yes (1)	No (2)					
BPD	Yes (1)	No (2)					
PDA needing medical/ surgical intervention	Yes (1)	No (2)					
Proven sepsis on culture (excluding CNS)	Yes (1)	No (2)					
Early ((≤3 days)							
Late (> 3 days)	Yes (1)	No (2)					
Highest mode of respiratory support By day 7	HFOV(1)	CMV(2)	CPAP(3)	Bipap(4)	Hiflow(5)	Prongs(6)	None(7)
By day 28	HFOV(1)	CMV(2)	CPAP(3)	Bipap(4)	Hiflow (5)	Prongs(6)	None(7)
Outcome	Discharged or transferred out (1)			Died (2)			
Duration of hospital stay (days)							

APPENDIX C: PLAGIARISM DECLARATION

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE I, **Angidi Pillay Mauree** (Student number: 307051), am a student registered for the degree of **MMed (Paeds)** in the academic year **2023**.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.

- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.

- I have followed the required conventions in referencing the thoughts and ideas of others.

- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection).

software indicating the level of plagiarism in my research document.

Signature: A. Mauree Date: 22 Feb 2023

APPENDIX D: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Angidi Pillay Mauree

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M200651

NAME: (Principal Investigator)	Dr Angidi Pillay Mauree
DEPARTMENT:	Paediatrics and Child Health Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Admission hypothermia in very low birth weight newborns at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	26/06/2020
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof D. Ballot
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	30/06/2020

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 Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **June** and will therefore be due in the month of **June** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

A-Maylew
Principal Investigator Signature

1/8/2020
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX E: TURNITIN REPORT

MMed Mauree Turnitin.docx

by Angidi Mauree

Submission date: 24-Feb-2023 02:47PM (UTC+0200)
Submission ID: 2021988388
File name: MMed_Mauree_Turnitin.docx (85.38K)
Word count: 5155
Character count: 27829

) newborns hypothermia especially within the first few hours after delivery.

prevalence, , and outcomes admission hypothermia VLBW newborns, quaternary Johannesburg, South Africa.

all VLBW newborns born over a seven) at CMJAH. Comparisons between hypothermic and normothermic newborns as well as between moderately-to-severely hypothermic and mildly hypothermic newborns were done. Multivariate binary logistic regression

: Mean gestational age and birthweight of enrolled newborns was 28.9 ± 2.7 weeks and 1097 ± 250 61.5 % of which 54.3% was mild hypothermia, 43.9 % was moderate hypothermia and 1.8 % was severe hypothermia. VLBW newborns have a birthweight < [aOR 1.37 (1.12-1.68)] and less likely to be associated with early onset sepsis [aOR 0.51 (0.30-0.88)]. VLBW newborns with moderate to severe hypothermia were less likely than those with mild hypothermia to have received antenatal steroids [aOR 0.66 (0.48-0.89)].

admission VLBW newborns reinforces the need for thermoprotective measures in this population.

(Word count: 247)

1.0 INTRODUCTION

, especially in premature newborns.(1, 2) There is a 28% increase in mortality in very low birth weight (VLBW) newborns for every one degree decrease in temperature below 36.0 °C.(3) The World Health Organization (WHO) recognizes that thermal care in the neonatal period is of utmost importance, yet hypothermia continues to be globally under-reported, under-recognized and poorly managed.(4)

1997, the WHO came up with a standardized definition of normothermia as being a temperature to < 36.5 °C was categorized into three subgroups the :

- Mild (.0 °C – and need to newborn look for a
- : 32.0 °C – 35.9 °C. Danger and need to immediately warm the newborn.
- Severe: < 32.0 °C. Grave outlook with requirement of urgent skilled care.

Globally, the incidence of admission hypothermia (AH) in VLBW newborns ranges between 31% and 78%.(3, 6, 7) The statistics from big cohorts in high income countries (HICs) are as follows: the Canadian Neonatal Network reported AH in 36% of preterm newborns < 33 weeks, the Effective Perinatal Intensive re in Europe showed AH in 54% of newborns < 32 weeks, 56% of VLBW newborns had AH 77% of VLBW newborns from a Taiwanese study had AH.(2, 8- AH in VLBW newborns 46% in South Africa, 54% in Brazil and 65% in Malaysia.(11-13)

There are several physiological risk factors for AH in premature newborns. If expose o the environment, premature newborns may experience a decrease in temperature postnatally .5 – .(6) Mechanisms of heat loss include ev poration, conduction, convection and radiation.(6) A premature newborn possesses a relatively (BSA) of up to four times that of an adult, decreased brown fat which is important for non-shivering thermogenesis and thinner skin with minimal stratum corneum.(1, 2, 8, 14) Prematurity has been shown to be the most important determinant of AH in VLBW newborns.(2) Other factors include an Apgar score < 7 at 5 minutes, newborns who had been resuscitated at birth or hypoglycemia at birth.(8, 12, 15-17) Studies in Brazil and Tanzania also showed that AH was more likely if a newborn was delivered outside of a hospital.(18, 19)

All of the above risk factors predispose to hypothermia which subsequently lead to increased risk of respiratory distress and need r surfactant administration.(2, 20) AH is also associated with complications such as sepsis,).(1, 2, 9) VLBW newborns with AH have longer hospital stays and higher mortality rates as compared to newborns with normothermia on admission.(2, 19, 20)

about AH using the WH classification in VLBW newborns in LMICs, particularly in Africa. A study carried out in 2016 Academic reported prevalence 46 % of AH in VLBW newborns and

some of the associated factors relevant to AH in VLBW newborns in the South African context.(12)

This study aimed to review AH in VLBW newborns neonatal unit South Africa – an upper middle-income country.

2.0

, descriptive from study population included all VLBW newborns delivered at CMJAH as well as VLBW newborns who were transferred in within 24 hours post-delivery. Newborns with no record of initial admission temperature were excluded. Newborns with specific congenital abnormalities causing an increased risk of evaporative losses (e.g., myelomeningocele and abdominal wall defects) were also excluded.

Setting

CMJAH quaternary neonatal unit consists of 104 beds, including levels 1 t of neonatal care. These levels respectively refer to a well newborn nursery, a nursery offering , a and a .(21) The unit is attached to an obstetric unit within the hospital and also functions as a referral center for surrounding clinics and hospitals.

tabase

analysis at CMJA computerized for clinical audit and quality improvement purposes and .(22, 23) was upon discharge, transfer or demise of the newborn from the neonatal unit. The data was checked and verified at several stages of collection before being entered into the database.

Variables

Compiled maternal variables included age, antenatal care attendance, multiple pregnancy, antenatal steroids, chorioamnionitis and Human Immunodeficiency Virus (HIV) status. Newborn characteristics included temperature on admission, sex, birthweight, gestational age, delivery mode, place of birth, Apgar score at 1, 5 and 10 minutes, highest delivery room resuscitation intervention, complications after delivery, duration of hospital stay and outcome on discharge.

The total sample was analyzed for baseline maternal and neonatal characteristics and then comparisons were drawn between the normothermia and the hypothermia subgroups. The hypothermia group was further divided into the mild hypothermia subgroup and a combined moderate-to-severe hypothermia subgroup for further analysis to be made.

efinitions

- positive if early- and late-onset after 72 hours postnatally.
- Necrotizing enterocolitis (the Bell's criteria.(24)
- as IVH or according to criteria.(25)
- Respiratory distress syndrome (RDS) was diagnosed in premature newborns requiring more than 40% FiO_2 after one hour of delivery with signs of respiratory distress and requiring surfactant use.
- Patent ductus arteriosus (PDA) was considered significant in newborns requiring medical and/or surgical intervention.
- Retinopathy more.(26)
- Bronchopulmonary dysplasia (BPD) referred to newborns needing oxygen at 28 postnatal days.

then). assessed. analyzed cases with whereby no admission temperature was recorded were excluded. riables interquartile ranges skewed variables. Categorical variables were and a compared using independent t-tests. Non-parametric tests such as the student t-test . Associations with hypothermia .1) further with multivariate analysis.

granted ethics number: M200651). and individual .

3.0 RESULTS

There was a total of 3 478 VLBW newborns eligible over the seven-year study period. We enrolled 2 678 (77.0%) newborns into the study after excluding 741 for no recorded temperature, 10 for congenital abnormalities associated with increased heat loss and 49 for presenting to CMJAH more than 24 hours post-delivery (Figure 1).

Of the enrolled newborns, 61.5% (1 648/2 678) of them had hypothermia on admission, of whom 54.3% (895/1 648), 43.9% (723/1 648) and 1.8% (30/1 648) had mild, moderate and severe hypothermia respectively.

The mean (standard deviation (SD)) age of the mothers was 28 (9) years. Slightly more than three out of every four mothers (77.6%; 2 077/2 678) had received antenatal care and 46% (1 233/2 678)

had been administered antenatal steroids. HIV positivity among this maternal cohort was 30.2% (785/2 678). Chorioamnionitis was diagnosed in 3% (81/2 678) of the mothers. There was 17.8 % (473/2 678) of mothers with multiparous pregnancies.

The mean birthweight and gestational age of the newborns was 1 097 (±250) grams and 28.9 (±2.7) weeks respectively. Most newborns were born at CMJAH (87.4%; 2 335/2 673), were female (53.1%; 1 422/2 678) and delivered by Caesarean Section (58.1%; 1 551/2 667). There were 3.3% (17/523) newborns with HIV.

Of the newborns who required resuscitation in the delivery room, the majority (85.1%; 2 279/2 678) necessitated oxygen (see Table 1 for a breakdown of the different types of resuscitation). After stabilization, the majority of the newborns (92.5%; 2 478/2 678) needed respiratory support at some point during their stay. A tenth of the newborns (9.9%; 265/2 678) developed metabolic acidosis (base excess < -16) while hypoglycemia (blood glucose< 2.6 mmol/L) was found in 14.3 % (384/2 678) of the newborns.

Nine out of every 10 (89.2%; 2 389/2 678) newborns developed RDS and seven out of 10 (70.8%; 1 895/2 678) newborns required surfactant administration. NEC was found in 7.7% (207/2 678) of newborns, 4.5% (35/780) of the newborns who had a documented ophthalmologic screen were found to have ROP, approximately one out of 10 (257/2 678) newborns was diagnosed with a PDA and 17.6 % (270/ 1 531) of the newborns who had a cranial ultrasound performed were found to have IVH. There was a lower proportion of early onset sepsis (2.4%; 64/2 678) as compared to late onset sepsis (22.4%; 600/2 678).

The median (interquartile range) stay of the newborns was of 27 (34) days with a range of 0 to 234 days. About a quarter (24.5%; 655/2 678) of the newborns required oxygen at day 28 of life. The mortality rate was 30.4% (813/2 678) with less than one in twenty (4.4%; 36/813) of those dying doing so in the delivery room.

Comparing newborns in the hypothermia subgroup to newborns in the normothermia subgroup

Out of all the newborns, there were 1648 (61.5%) newborns in the hyp[30]ermia subgroup as compared to 1012 (37.8%) newborns in the normothermia subgroup. (±1.1) ⁰ 36.7 (±0.2) ºC in the hypothermia and normothermia subgroups respectively.

the two subgroups. Newborns who were hypothermic were more likely to have a birthweight < 1000 g [37.0% versus 29.2%, OR 1.42 (1.20-1.67), p<0.001] and to being delivered at < 30 weeks of gestation [62.7% versus 57.4%, OR 1.05 (1.02-1.08), p 0.007]. This study showed that a newborn with hypothermia was found to have a lower birthweight (1080 vs. 1126.8 g) and a lower gestation (28.8 weeks vs. 29.1 weeks) than a normothermic newborn. sex, whether pregnancy involved multiple gestation, in the mode of delivery or where the delivery occurred.

Newborns with hypothermia were more [26] < 7 [23.7% versus 18.9%, OR 1.34 (1.10-1.64), p 0.004] and Apgar score at 10 minutes [10.4% versus 8.6%, OR 1.24(0.92-1.65), p 0.15]. With regard to

resuscitation in the delivery room, the study showed that there was an association between hypothermia and use of cardiac compressions [11.5% versus 8.9%, OR 1.33 (1.02-1.73), .035]. usage different modalities of respiratory support postnatally between the two subgroups.

This study showed that a hypothermic newborn was more likely to develop metabolic acidosis [10.9% versus 8.2%, OR 1.37 (1.05-1.80), .022]. marked morbidities namely RDS, NEC, ROP, IVH, PDA, sepsis, or BPD.

A VLBW newborn with hypothermia more likely to die as opposed to someone with normothermia [32% versus 27.7%, OR 1.23 (1.04-1.46), .019]. length hospital stay: hypothermic newborns had a median (IQR) stay of 27 (36) days as opposed to normothermic newborns who stayed for 28 (30) days [OR 1.00 (0.999-1.005), p 0.16].

Variables with .1 multivariate model.

Out of categorical variables ELBW vs birthweight of 1000-1500g, gestation < 30 weeks vs gestation ≥ 30 weeks and the continuous variables of birthweight and gestation, the categorical variable of ELBW vs birthweight of 1000-1500 g was chosen as it was the most significant one.

then born with ELBW, male sex, Apgar at 5 minutes being < 7, having CPR in the delivery room, presence of metabolic acidosis RDS, early onset sepsis and death on the likelihood that the newborns will have hypothermia. (1962) .003. (8) = 34.898 .001. 1.9% (R^2) admission temperature 61. 98. 2%, .5% 54.3%. , only birthweight early onset sepsis independently associated with AH. A newborn with hypothermia was 1.37 (95 % CI: 1.12-1.68) more likely than one with normothermia to be born with a birthweight < 1000 g. Early onset sepsis was less likely in those with hypothermia as compared to those with normothermia (aOR 0.51, 95% CI: 0.30-0.88).

Comparing newborns in the moderate to severe hypothermia subgroup to newborns in the mild hypothermia subgroup.

The mean (SD) admission temperature in the moderately to severely hypothermic and the mildly hypothermic subgroups was 34.8 (1.3) º C and 36.2 (0.2) º C respectively. Out of the newborns with hypothermia, 45.7% (753/1 648) were in the moderate to severe hypothermia subgroup and 54.3 % (895/1 648) were in the mild hypothermia subgroup. Mothers to newborns with moderate to severe hypothermia were less likely to have received antenatal care [72.1% versus 80.8%, OR 0.62 (0.49-0.77), p <0.001] or antenatal steroids [37.5% versus 51.5%, OR 0.56 (0.46-0.69), p<0.001] as compared to mothers with newborns with mild hypothermia.

The newborns with moderate to severe hypothermia as opposed to those with mild hypothermia were also found to be more likely associated with having been born with an extremely low birth weight [41.6% versus 33.1%, OR 1.44 (1.18-1.76), p <0.001] and to have a gestation of less than thirty weeks [66.8% versus 59.2%, OR 1.39 (1.13-1.70), p 0.002]. Newborns with moderate to severe hypothermia were less likely to have been delivered by caesarean section [50.3% versus 62.7%, OR 0.60 (0.50-0.73), p <0.001] or born at CMJAH [81.8% versus 91.9%, OR 0.39 (0.29-0.53), p <0.001] as opposed to a newborn with mild hypothermia.

Newborns in the moderate to severe hypothermia subgroup had significantly lower Apgar scores at five [28.7% versus 19.9%, OR 1.62 (1.28-2.06), p< 0.001] and ten minutes [14.1% versus 7.5%, OR 2.01 (1.42-2.84), p<0.001] than those with mild hypothermia. Those found to have moderate to severe hypothermia as compared to those with mild hypothermia were found to most likely require CPR [14.2% versus 9.2%, OR 1.64 (1.21-2.23), p 0.001] and intubation [3.6% versus 1.5%, OR 2.52 (1.29-4.93), .005] in the delivery room and more likely to develop metabolic acidosis [13.9% versus 8.4%, .77 (.30-.42), .001] IVH [20. 15%, .48 (.05-.08), .024]. Having late onset sepsis was less likely in those with moderate to severe hypothermia as compared to those with mild hypothermia (19.4% versus 23.6%, OR 0.78 (0.62-0.99), p 0.04].

VLBW newborns to hypothermia shorter median (IQR) length of hospital stay than those with mild hypothermia [25(39) days versus 27 (32) days, OR 1.005 (1.002- 1.009), p 0.006]. A VLBW newborn with moderate to severe hypothermia as compared to one with mild hypothermia was more likely to die [38.1% versus 26.8%, OR 1.68(1.36-2.07), p<0.001] and this was also significant in the delivery room [7% versus 2.1%, OR 3.52 (1.30-9.53), p 0.009].

Variables with .1 multivariate binomial model. Out of categorical variables ELBW vs birthweight of 1000- 1500g and gestation < 30 weeks vs gestation ≥ 30 weeks, the first variable was chosen as it was the most significant one.

likelihood moderate severe hypothermia as compared to mild hypothermia after taking into account if the newborn had antenatal care, antenatal steroids, having been born with ELBW, having been delivered via caesarean section, having been delivered at CMJAH, having had a recorded Apgar score of less than 7 at 5 and 10 minutes respectively, having had cardiac compressions and been intubated in the delivery room, having developed metabolic acidosis or intraventricular hemorrhage, having developed late onset sepsis, length of stay and dying.

(1962)

.002.

(14) = 25.35, .021. 4.3% (R^2) admission temperature 59.6 % 23. 85.9%, 55.2% 60.6%. 14 , only antenatal steroids . Those newborns with moderate or severe hypothermia were found to have a lower association with antenatal steroids than those with mild hypothermia. (OR 0.66)

4.0 DISCUSSION

y findings

[redacted] AH [redacted] VLBW newborns especially [redacted] LMICs. Our [redacted], carried out in a large academic quaternary hospital in Johannesburg, South Africa, shows that approximately three out of every five (61.5%) VLBW newborns were hypothermic on admission to the neonatal unit postdelivery. This is a higher prevalence than some of the reported rates in HICs but comparable to the studies done in LMICs.(8-11, 13, 16) There was a very small prevalence of VLBW newborns who were hyperthermic (0.7%).

Out of all the newborns with hypothermia, slightly less than half of them had moderate to severe hypothermia (45.7%). This is a particularly high percentage which shows that there could be more implementation of appropriate temperature regulation measures. Looking at the overall characteristics of the VLBW newborns, it could be appreciated that almost nine out of ten were born at CMJAH. It is worth noting that the study showed that almost 1 in 3 VLBW newborns passed away.

Comparing VLBW newborns with hypothermia to VLBW newborns with normothermia

In this study, VLBW newborns with AH as compared to those with normothermia were found to more likely be of ELBW (unadjusted OR 1.42) and to be of gestational age < 30 weeks (unadjusted OR 1.05). Adjusting for other independent variables still resulted in a newborn with birthweight < 1000 g being 1.37 times more likely to experience AH as opposed to a normal temperature. This was in accordance with other studies where a lower birthweight and gestational age were associated with admission hypothermia. (1, 2) Contributing reasons would entail all the physiological factors that predispose newborns to lose heat the more preterm they are.

AH was not associated with the newborn's gender, the mode of delivery and whether the child was born at CMJAH or transferred in within 24 hours postnatally. One similar study in South Africa had shown that AH was associated with vaginal delivery while another study from the USA had shown the association with being delivered by caesarean section. (10, 12) This study also did not show that AH was associated more with outborn patients coming to the referral center as evidenced by studies in Tanzania and Brazil and this might be due to our high proportion of newborns who are inborn in both subgroups. (18, 19)

This current study showed that maternal age, antenatal care or steroids and presence of chorioamnionitis did not have any association with AH.

This study showed that a newborn with AH was more likely to have an Apgar score of less than 7 at 5 minutes as opposed to someone with normothermia as supported by a study by Miller et al. (10). The interaction between Apgar score and temperature might be that hypothermia at birth leads to increased need for resuscitation and therefore a lower Apgar score at 5 minutes or that conversely resuscitation with a low Apgar score leads to uncovering the newborn and therefore hypothermia on the first recorded temperature.

Studies done in Africa by Demissie et al. (Ethiopia) or Ng'eny et al. (South Africa) have shown that there is an association between the need for resuscitation at birth and subsequent AH. Our study showed that a newborn who received cardiac compressions was associated with developing AH and this might be due to the fact that increased exposure for the compressions predispose to the cold.

AH has also been associated with metabolic acidosis whereby hypothermia causes peripheral vasoconstriction with increased oxygen demand leading to anaerobic metabolism and metabolic acidosis. (12, 14) This was found in our study but not supported when doing the logistic regression model.

Apart from the association between birthweight and admission hypothermia, the only other variable which had a significant association when doing the logistic regression model was early onset sepsis. Our study highlighted that newborns with hypothermia were less likely to develop early onset sepsis than those with normothermia. A potential explanation could be that there is closer supervision of newborns diagnosed with hypothermia once they get admitted to the neonatal unit.

Comparing VLBW newborns with moderate to severe hypothermia to VLBW newborns with mild hypothermia

We found that the odds of developing moderate to severe hypothermia were significantly lower by using antenatal steroids and this is supported by Miller et al. (10) This is probably attributed to the fact that a mother who had received steroids antenatally was more likely to have a newborn with better lung function; leading to less risk of respiratory distress at birth and less need for resuscitation.

This study also showed that a VLBW newborn with moderate to severe hypothermia as compared to mild hypothermia was less likely to have a mother who attended a clinic antenatally (OR 0.62) but this was not statistically significant when the multivariate logistic regression was carried out. This still highlights the importance of the mother making an early appointment during pregnancy and to follow up regularly.

Our study showed that the lower the birthweight and gestational age, there was an association with moderate to severe hypothermia as opposed to normothermia. This was however not supported by the multivariate logistic regression. Newborns born by vaginal delivery were more likely to have moderate or severe hypothermia and this could be due to the sub-optimal temperature in the delivery room which is an open room as compared to the better controlled temperature in the operating theatres. There is also a dedicated member from the neonatal team at the delivery of a VLBW newborn in theatre as compared to at a vaginal delivery; allowing for implementation of thermoprotective measures more promptly in the first case. Newborns who were referred to CMJAH from other units were more likely to experience moderate to severe hypothermia than mild hypothermia and this is most likely linked with suboptimal incubator temperature or inadequate wrapping during transfer. Being delivered outborn was a risk factor as suggested by studies in other LMICs such as Brazil, Ethiopia and Tanzania. (16, 18, 19)

The more severe the hypothermia, this was associated with an Apgar score of less than 7 at 5 minutes and at 10 minutes and an increased association with requiring chest compressions or needing to be endotracheally intubated. Resuscitation usually means that the newborn has to be fully exposed to gain intravenous access and for compressions to be done and this leads to the newborn losing even more heat on top of already being predisposed as compared to a term newborn.

In terms of complications, being moderately to severely hypothermic was associated with metabolic acidosis (OR 1.77) and IVH (OR 1.48). The development of metabolic acidosis was

supported by other studies and could be explained by the increased oxygen demand leading to anaerobic metabolism in a newborn with a lower temperature. The etiology of IVH is multifactorial and the association with a newborn with moderate to severe hypothermia could be due to that newborn requiring resuscitation.

This study surprisingly demonstrated that there was a lower association of late onset sepsis in the VLBW newborn with moderate to severe hypothermia. This might be linked to the higher association of death in that group during the hospital stay (OR 1.68). Out of all the deaths, it was found that a newborn with moderate to severe hypothermia was 3.5 times more likely to die in the delivery room than a newborn with mild hypothermia.

The only variable which was found to be statistically significant after taking into account the independent variables, was the use of antenatal steroids which was found to decrease the severity of the degree of hypothermia in a VLBW newborn. This further reinforces the administration of any dose of steroids for the eligible mothers.

5.0 STUDY LIMITATIONS

The retrospective nature of this study meant that establishing temporal relationship between some variables was difficult and there was additionally incomplete or missing data. A fifth of newborns did not have their initial temperature recor[16] and this large proportion could alter the overall results. The inherent risk of bias brought by been minimized by large sample size.

Furthermore, some information such as the exact time of when the first temperature or first glucose measurement was recorded postnatally was not routinely collected. We also hope that the first temperature value was actually entered into the database in the event of several temperature recordings within the first hour. The room temperature to which each of the VLBW newborn was exposed on delivery would also be a variable that would be worth recording and should be at a minimum of 25°C as recommended by the WHO and definitely not always achieved. There was a high number of unknown HIV results which might be attributed to information captured at time of delivery not being subsequently updated.

The protocol of measuring temperature is usually done on the skin in the unit [5] the .

There might have been inter-observer variability in the diagnosis of IVH and Ballard scoring. We can only comment on associations in this study.

6.0 CONCLUSIONS AND RECOMMENDATIONS

This study showed a high prevalence of admission hypothermia in VLBW newborns. AH was associated with a lower birthweight but was inversely associated with early onset sepsis. This of antenatal steroids less moderate to severe hypothermia as compared to mild hypothermia.

This highlights the importance of ensuring that all thermoprotective factors are implemented as soon as a newborn is delivered while following the guidelines by the Resuscitation Council of Southern Africa.(27)

There should also be a general consensus with all studies looking at admission hypothermia in newborns to abide by the WHO criteria of subcategorization of hypothermia.

There should be ongoing quality improvement programs aimed at educating healthcare practitioners about rapidly recognizing and implementing measures to prevent or address AH especially in VLBW newborns. Further studies could be carried out to focus on comparing data before and after any interventions aimed at addressing hypothermia and also look at associations with .

Further could focus the difference in AH between daytime and nighttime and also between different seasons. One could also look at the relation between number of doses of antenatal steroids and its effect on hypothermia (moderate to severe versus mild).

Contribution to the field statement

APM's .

: APM conceptualized , collected data, carried out data analysis, ; DEB RS supervised the study, a self- undertaking.

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