A REVIEW OF NEONATAL OUTCOMES TO DISCHARGE, OF PERINATAL ASPHYXIA AND THE USE OF INDUCED HYPOTHERMIA AS A TREATMENT MODALITY, AT A TERTIARY CENTRE IN SOUTH AFRICA

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Declaration

I hereby declare that this research report has been submitted for the Degree of Master of Medicine in Paediatrics to the University of Witwatersrand, Johannesburg. It has not been submitted by me or anyone else for a degree at this or any other university. This is my own work and materials consulted have been properly acknowledged.

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Dr R Simpson

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Abstract

Background: Perinatal asphyxia (PA) is a significant cause of death and disability. Induced hypothermia (IH) has become crucial in it's the management with improved mortality and morbidity, however is it a viable in low to middle income countries.

Objectives: To review the neonatal clinical, demographic characteristics and outcomes of perinatal asphyxia with IH as a treatment modality in Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)

Methods: A descriptive retrospective analysis of an established database. Neonates admitted between January 2013 and July 2017 with a birth weight >1800g and a 5-minute Apgar score ≤5, with features of perinatal asphyxia, were included.

Results: N=639 neonates with 399 males (62.4%). The majority of the neonates were inborn (499/639, 84.5%). 527 neonates (82.5%) diagnosed HIE, with majority grade two, 43.3%. The overall survival rate was 87.1% to discharge. An increased incidence of HIE 7.7 /1000 live births since previous study. 33.3% neonates received IH. IH side effects and death were not significantly increased. Incidence of death was increased with the presence of seizures, MSL, MAS, PPHN, HIE, and grade 3 HIE classification ($p < 0.05$).

Conclusion: IH did not increase survival rates significantly but a study to assess the impact on the morbidity is warranted. IH for severe HIE and possible adjunct therapies should be considered. The crude use of an Apgar <7 at 10-minutes could be used as a poor prognostic factor. The high incidence rate echoes' the need for a set criterion for PA in resource limited settings to record the incidence and set a benchmark for improvement.

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Nomenclature (Abbreviations)

a-EEG	amplitude- electroencephalography
BBA	Born Before Arrival
C/S	Caesarean Section
CHB	Chris Hani Baragwanath Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
HIE	Hypoxic Ischaemic Encephalopathy
IH	Induced hypothermia
LMIC	Low to middle income countries
MAS	Meconium Aspiration Syndrome
MRI	Magnetic Resonance Imaging
MSL	Meconium Stained Liquor
NICU	Neonatal Intensive Care Unit
NNE	Neonatal encephalopathy
PA	Perinatal Asphyxia
PPHN	Persistent Pulmonary Hypertension of the newborn
SAPA	South African Paediatric Association
TCH	Tygerberg Children's hospital

Chapter 1 - Submissable Paper

A REVIEW OF NEONATAL OUTCOMES TO DISCHARGE, OF PERINATAL ASPHYXIA AND THE USE OF INDUCED HYPOTHERMIA AS A TREATMENT MODALITY, AT A TERTIARY CENTRE IN SOUTH AFRICA

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***Key Words:** Hypoxic Ischemic Encephalopathy;*
Perinatal Asphyxia
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Introduction

Every year, perinatal and neonatal deaths account for 44% of the nine million deaths globally for children under 5 years of age. (1) Perinatal asphyxia accounts for 23% of those deaths, which highlights the global impact of this problem. (1) Not only does perinatal asphyxia contribute to the high mortality rates but it also contributes greatly to the high morbidity rates, since those that survive may have serious neurological sequelae ranging from developmental delay to severe cerebral palsy. (2,3,4)

Asphyxia is defined as any interruption in oxygen delivery, resulting in hypoxaemia, hypercapnia and metabolic acidosis. (3,4,5) Hypoxic ischemic encephalopathy (HIE) is a consequence of perinatal asphyxia and presents with neurological abnormalities on the first day of life. However, once signs and symptoms of HIE are present, the therapeutic window of opportunity for induced hypothermia (IH) has been missed, which emphasizes the importance of diagnosis and grading of HIE early. One of the difficulties with diagnosing HIE, is the lack of additional resources to assist the diagnosis such as blood gas showing metabolic acidosis, amplitude EEG and MRI to show intrapartum asphyxia. (6).

A previous study at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) assessing the outcomes of perinatal asphyxia during the period of 1 January 2006 to 31 December 2011, revealed an incidence of perinatal asphyxia of 4.7 per 1000 live births, as well as an overall survival rate of 86.7%. (4) Similarly, a study performed at Chris Hani Baragwanath Hospital (CHB) in 2011 revealed an incidence of asphyxia of 8.7 to 15.2 per 1000 live births, with a mortality rate of 7.58%. (3) These studies highlight that perinatal asphyxia is a common cause of death in neonates in South Africa.

It has been established that HIE at a cellular level occurs in two phases following a reversible hypoxic ischaemic global insult. Phase one is the primary neuronal death due to primary energy failure. (7) Phase two, expected to occur six hours later from the initial insult, is known as delayed neuronal death which is associated with encephalopathy and increased seizure activity. IH is used to limit the effects of phase two. (7) The aim of IH is to lower the temperature of the vulnerable brain structures such as the basal ganglia, to 32 - 34°C. Whole body cooling and selective head cooling are two methods of IH that have been shown to be effective. (7) In a Cochrane Review of IH in 2013, eight randomised controlled trials were included. IH resulted in a statistically significant and clinically important reduction in the combined outcome of

mortality or major neurodevelopmental disability to 18 months of age, with a number needed to treat of 7 (95% CI 4, 14). (7) The review concluded that IH's benefits far outweighed the risks of adverse side effects. (5,7)

Should IH be considered a viable treatment option in low to middle income countries (LMIC) with low resource settings with limited access to neonatal intensive care unit (NICU), low budget for expensive IH machinery, amplitude-electroencephalography (a-EEG), and lack of trained health care staff. A study performed at Tygerberg Children's hospital (TCH), a tertiary centre in South Africa, revealed it was a feasible option in low resource settings. The study replicated similar results, with a reduction of mortality and morbidity, to developed countries, however it requires a strict protocol and training of health care staff. (8) TCH also used the Tecitherm TSmed 200 N system which is an expensive IH machine and the study was performed in a NICU setting with a high nurse to patient ratio (2;1), which may not be available in many LMIC health centres. (8)

A systematic review and meta-analysis of IH for neonatal encephalopathy (NNE) in LMIC was performed, which assessed the use of low cost IH devices such as frozen gel packs and water bottles. This review showed that there was no statistically significant reduction in neonatal mortality and also there was a five times higher mortality rate in IH patients compared to those that received standard treatment. (9) Even though this review questions whether IH should be offered in LMIC's one should consider that these results could be due to the low technology devices and the lack of intensive nursing monitoring, resulting in fluctuations in temperature which is potentially dangerous and non-neuroprotective. (5,9)

These studies highlight the necessity to evaluate each centre individually and whether IH is achieving comparable outcomes to developed countries, even when NICU facilities are not often available or provided to HIE neonates. Prior to offering IH there should be suitable equipment, the training of health care providers and a strict protocol of the IH requirements and procedure adapted from international guidelines. (5,8,9)

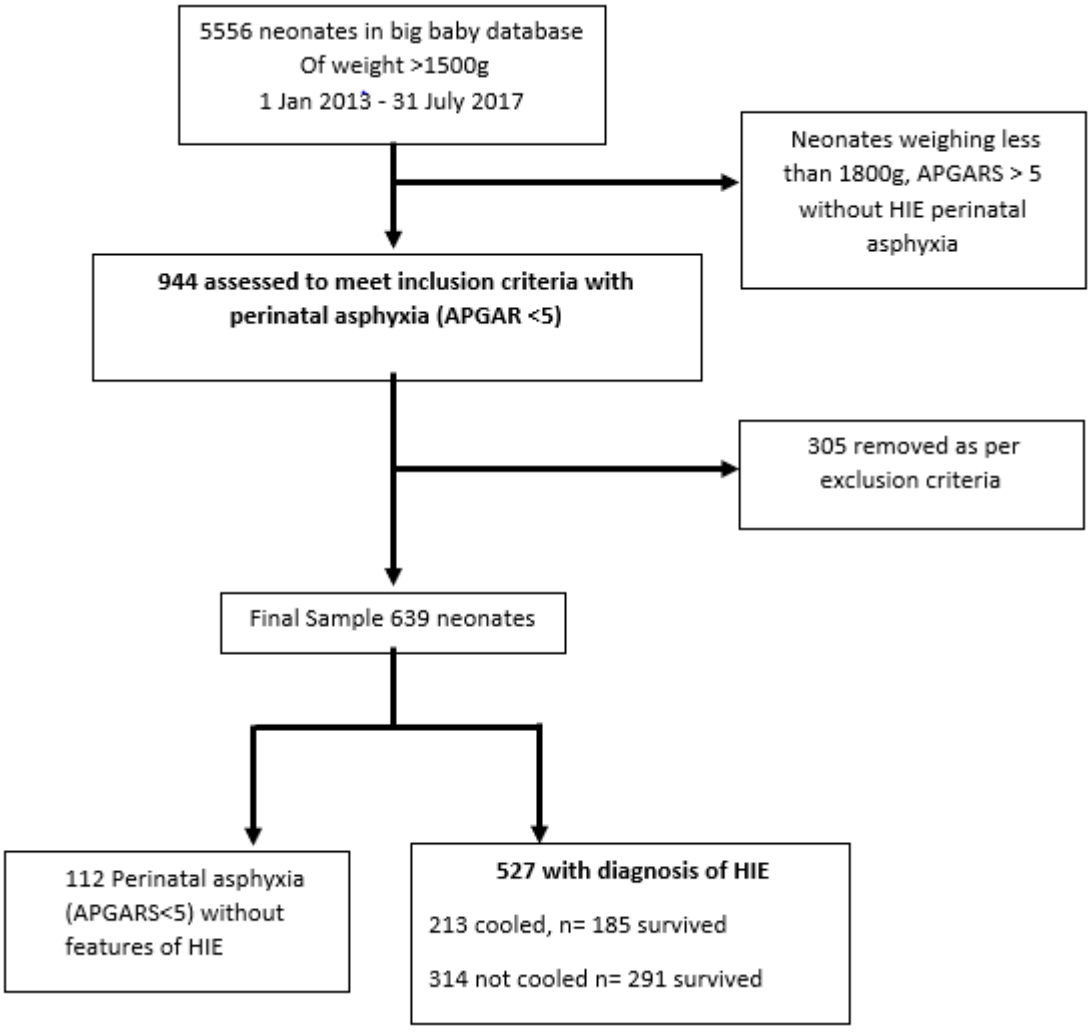
The primary objectives of the current study were to characterise neonates diagnosed with PA, report the incidences of PA, HIE and IH at CMJAH. Secondary objectives were to investigate the possible reported side effects of IH, evaluate the viability of IH as a treatment modality at CMJAH, and to compare this study's results to those previously reported at the same centre.

Methods

a) Subjects

This study was a retrospective descriptive analysis, reviewing an existing database of all neonates admitted at CMJAH from 1 January 2013 to 31 July 2017. Neonates were included in the sample if their birth weight was greater than 1800g, and had evidence of perinatal asphyxia. HIE was diagnosed and assigned a grade by the attending doctor. Neonates with possible causes of low Apgar scores other than perinatal asphyxia, major birth defects e.g. Chromosomal abnormalities and missing significant information were excluded. (See Figure 1).

Figure 1: Final data set refinement graph



b) Definitions

Perinatal asphyxia was defined by TOBY criteria, presences of at least one of the following: 5-minute Apgar score of 6 or less, birth resuscitation for more than 10 minutes, metabolic acidosis within the first hour of life (BE>-16mmol/l). (10) HIE defined using the Sarnat

classification, to identify and grade HIE. (11) Meconium aspiration syndrome(MAS) was defined as presence of meconium stained liquor(MSL), need for oxygen and radiology changes. Persistent pulmonary hypertension (PPHN) was confirmed by echocardiography. (11)

c) Methods

Patient information was obtained from the existing computerized neonatal database at CMJAH. The data was managed using Research Electronic Data Capture (REDCap™) hosted at The University of the Witwatersrand. REDCap™ is a secure web-based program that has been designed to assist in the collection of data for clinical audits and research studies. Standard information was collected by the attending medical staff on patient discharge and entered into the database with several verifications performed at different stages. The information included was maternal and neonatal demographics, Apgar scores at 1, 5 and 10 minutes, presence of seizures, presence and grade of HIE, duration of hospital stay, cerebral IH, presence of MSL, MAS, PPHN and presence of culture confirmed early (before or on day 3) or late neonatal sepsis (beyond day 3).

Neonates with PA were not routinely ventilated, because of resource limitations of NICU facilities. These neonates received supplemental oxygen, fluids, anticonvulsants, nutrition and antibiotics as required.

IH was initiated for neonates that qualified as per CMJAH cooling protocol criteria and at the discretion of the attending doctor in consultation with a paediatrician. The Tecithem TSmed 220 N cooling system was used. No MRI and a-EEG facilities were available during the study period. The CMJAH cooling criteria modified from the TOBY trial included: gestational age greater than 34 weeks; birth weight greater than 2kg; Apgar score 5 or less; or the need for resuscitation for more than ten minutes; metabolic acidosis with pH less than 7 or base deficit of greater than 16mmol/L on blood gas within sixty minutes of life; presence of encephalopathy; within 6 hours of life post-delivery and Thompson score of greater than or equal to 7 which was only initiated towards the end of this study. (10,11) CMJAH did not routinely offer IH to HIE grade 3's due to the resource constraints and the likely poor prognosis associated with this group. (4,11)

d) Statistical Analysis

Data was compiled in an MS Excel (Microsoft, USA) spreadsheet which was then imported into statistical software package SPSS version 25 (IBM, USA) for analysis. The continuous

variables were analysed using descriptive study methods and expressed as means, medians and interquartile range (IQR). Survivors to discharge and non-survivors as well as IH and non-IH neonates were compared. Categorical variables were described and compared using a Chi Square analysis and were expressed as frequencies and percentages, continuous variables were compared using unpaired t tests or Mann Whitney U analysis dependent on the distribution of the data. A p-value of <0.05 was considered statistically significant.

e) Ethics

The study was approved by the Human Research Ethics Committee (Medical) of the University of Witwatersrand (clearance certificate number M170116).

Results

a.) Clinical and demographic characteristics of total sample

A total of 639 PA neonates fulfilled all criteria (see Figure 1), 240 females (37.6%) and 399 males (62.4%). The mean birth weight ±SD was 3 006.35 ± 564.0g, and the mean ±SD gestational age was 38.35 ± 2.4 weeks. The mean ±SD maternal age was 27.08 ± 6.0 years and mean parity was 1 (interquartile range 0 – 6). Clinical and demographic characteristics are displayed in Table 1 and 2. The majority of the babies were born at CMJAH (499/639, 84.5%) and by normal vaginal delivery (285/639, 44.6%) but of note emergency caesarean section (C/S) was also a common mode of delivery 248/639 (38.8%). Most mothers received antenatal care 540/639 (84.5%) and were HIV negative 471 (73.7%). A total of 527 neonates (82.5%) had a diagnosis of HIE. A HIE grade was assigned to 472/527 (89.5%) as per the Sarnat classification with majority classed as grade two 228/527 (43.3%). . See table 3

b.) Survival rate and Incidence

There were an estimated 1225 live births per month (2016 and 2017 delivery figures) from CMJAH and two major midwife obstetric units affiliated with the hospital. The incidence of HIE is estimated at 7.7 per 1000 live births. Perinatal asphyxia rate of 9.3 per 1000 live births. (11) (3) The overall survival rate to discharge of PA was 557/639 (87.1%) and HIE was 447/527 (85.2%) . (See Table 1). The estimated mortality rates were 1.2 per 1 000 live births for PA and HIE.

c.) Survivors vs non-survivor's neonates

This comparison generated statistically significant differences with an increased incidence of death if a neonate had the presence of seizures, MSL, MAS, PPHN, HIE, and grade 3 HIE classification in categorical variables (p-value <0.001). Of the continuous variables, the duration of stay was prolonged in the survivors with a median 6 vs 2 days (p-value 0.006). (See Table 4 and 5)

Table 1 Comparison of categorical variables of Survivor vs. Non-survivors

Characteristic		**Total (N=639)**		**Survivor (N=553)**		**Non-Survivor (N=82)**		**P Value**
		n	**% / IQR**	***N***	**% / IQR**	***n***	**% / IQR**	
Antenatal Care		540	84.5%	469	84.8%	67	81.7%	0.843
Place of delivery	Inborn	499	78.1%	438	79.2%	57	69.5%	0.630
	Out born	126	19.7%	104	18.8%	22	26.8%	
	BBA	7	1.1%	6	1.1%	1	1.2%	
Maternal HIV		154	24.1%	136	24.6%	18	22.0%	0.318
Positive Birth HIV PCR		2	0.3%	1	0.18%	1	1.2%	0.046
Mode of delivery		285	44.6%	238	43.0%	45	54.9%	0.219
NVD								
	CS emergency	248	38.8%	217	39.2%	30	36.6%	
	CS Elective	43	6.7%	40	7.2%	3	3.7%	
	Vaginal breech	21	3.3%	18	3.3%	2	2.4%	
	Assisted vaginal delivery	35	5.5%	33	6.0%	2	2.4%	
Gender	Female	240	37.6%	213	38.5%	26	31.7%	0.431
	Male	399	62.4%	340	61.5%	56	68.3%	
Median Apgar	1 min	3	0-9	3	0-9	2	0-9	<0.001
	5 min	5	0-10	5	0-10	4	1-9	<0.001
	10 min	7	1-10	7	1-10	6	2-10	<0.001
Birth Resuscitation								
	Bag-mask Ventilation	453	70.9%	390	70.5%	59	72.0%	0.422
	Chest Compression	148	23.2%	120	21.7%	27	32.9%	0.079
	Adrenalin	20	3.1%	17	3.1%	3	3.7%	0.900
Presence of seizures		127	19.9%	100	18.1%	26	31.7%	0.015
Cooling		213	33.3%	187	33.8%	25	30.5%	0.385
MSL		108	16.9%	81/450	18.%	21/75	28.0%	0.006
MAS		86	13.4%	64	11.6%	22	26.8%	0.001
PPHN		20	3.1%	11	2.0%	9	11.0%	<0.001
Culture-positive sepsis before day 3		13	2.0%	13	2.4%	0	0.0%	0.704
Culture-positive sepsis after day 3		26	4.1%	23	4.1%	3	3.7%	0.897
HIE grade	1	158/528	30.0%	154/449	34.3%	3/75	4.0%	<0.001
	2	228/528	43.1%	205/449	45.7%	21/75	28.0%	
	3	86/528	16.3%	43/449	9.6%	43/75	57.3%	
	Not specified	56/528	10.6%	47/449	10.5%	8/75	10.7%	

Table 2: Comparison of survivors and non-survivors for continuous variables

Characteristic	Total (N=639)		Survivors (N=553)		Non-survivors (N=82)		P Value
	Mean/ Median	SD/ IQR	Mean/ Median	SD/ IQR	Mean/ Median	SD /IQR	
Maternal Age (years)	27.08	6.06	27.15	6.14	26.45	5.39	0.139
Gestational Age (weeks)	38.35	2.37	38.30	2.34	38.64	2.60	0.240
Birth Weight (g)	3006.35	564.39	2996.24	561.51	3062.30	593.56	0.719
Thomson Score	8.48	4.20	8.10	4.09	12.71	3.86	0.611
Duration of stay	5.00	(0-89)	6.00	(0-89)	2.00	(0-21)	<0.001
Discharge weight	3014.58	572.02	3006.60	567.20	3083.54	609.82	0.728

d.) Induced Hypothermia vs Non-Induced Hypothermia HIE neonates

The comparison between IH and non-IH neonates yielded no statistically significant difference in maternal characteristics, mode of delivery, or resuscitation requirements. (See Table 3) Of the 527 HIE neonates, 213 (40.4%%) received IH of which 12 (2.3%) missed IH due to a machine being unavailable. The survival rate of IH 187/213 (87.8%) vs. non-IH 262/314 (83.4%) was non-significant. IH neonates are mostly HIE grade two (70.4 % vs. 24.8%). The analysis of the continuous variables yielded a statistically significant difference in gestational age in weeks, and discharge weight (p-value<0.001). There was no significant increase in IH side effects of thrombocytopenia, sepsis and death. (See Table 3)

e.) Comparison to Padachyee et al previous study

In comparison to previous study performed by Padachyee et al, the overall survival rate from 390/450 (86.7%) vs. 557/639 (87.1%) has remained unchanged (p-value 0.81). Since that study, IH has become a component of management of HIE in CMJAH and hence an increase in neonates that received IH from 0.4% to 40.3% neonates. Also, an improvement in documenting the grade of HIE according to the Sarnat criteria was seen when compared to the previous study (45.5% vs 89.4%). The rates per 1000 live births of perinatal asphyxia (9.3 vs. 4.7) (p-value 0.21) and HIE (7.7 vs. 3.6) have increased (p-value 0.25). An increase in emergency C/S was seen (26.7% vs. 38.8%) and attendance of antenatal care 68% vs 84.5%. Duration of stay was increased from median 4 (IQR 0-76) to 5 (IQR 0-89).

Table 3: Comparison of categorical variables of induced hypothermia vs. non-induced hypothermia neonates

Characteristic	Total Hypoxic Ischemic Encephalopathy (N=527)		Induced hypothermia (N=213)		Non-induced hypothermia (N=314)		P Value
	N	%	*N*	%	*N*	%	*N*
Attended Antenatal Care	443	84.1%	184	86.4%	259	82.5%	0.116
Place of delivery							0.212
Inborn	401	76.1%	173	81.2%	228	72.6%	
Out born	113	21.5%	27	12.7%	76	24.2%	
BBA	7	1.3%	2	0.9%	5	1.6%	
Positive Maternal HIV	125	23.7%	50	23.5%	75	23.9%	0.049
Positive Birth HIV PCR	1	0.2%	1	0.5%	0	0%	0.072
Mode of delivery							0.154
NVD	245	46.5%	105	49.3%	140	44.5%	
CS emergency	196	37.2%	75	35.2%	121	40.6%	
CS Elective	27	6.6%	14	6.6%	13	4.1%	
Vaginal breech	20	1.9%	4	1.9%	16	5.1%	
Assisted vaginal delivery	32	6.6%	14	6.6%	18	5.7%	
Gender							0.688
Female	195	37.0%	81	38.0%	114	36.3%	
Male	332	63.0%	132	62.0%	200	63.7%	
Birth Resuscitation							
Bag-mask Ventilation	371	70.4%	156	73.2%	213	67.8%	0.239
Chest Compression	124	23.5%	56	26.3%	68	21.7%	0.218
Adrenalin	19	3.6%	7	3.3%	12	3.8%	0.746
Presence of seizures	126	23.9%	63	29.6%	63	20.1%	0.012
MSL	102	19.4%	35	16.4%	67	21.3%	0.365
PPHN	13	2.5%	4	1.9%	9	2.9%	0.473
Culture-positive sepsis before day 3	8	1.5%	4	1.9%	12	3.8%	0.110
Culture-positive sepsis after day 3	20	3.8%	12	5.6%	8	2.5%	0.069
Thrombocytopenia	15	3.8%	8	3.8%	7	1.6%	0.096
HIE grade							<0.001
1	158	30.0%	25	11.7%	133	42.4%	
2	228	43.3%	150	70.4%	78	24.8%	
3	86	16.3%	32	15%	54	17.2%	
Not Specified	55	10.4%	6	2.8%	49	15.7%	
Outcomes							0.273
Discharge	439	83.3%	185	86.9%	254	81.0%	
Demised	75	14.2%	25	11.7%	50	15.9%	
Transferred to surgical/another hospitals	10	1.9%	2	0.9%	8	2.5%	

Table 4: Comparison of induced hypothermia and non-induced hypothermia neonates for continuous variables

Characteristic	IH (N=213)		Non-IH (N=314)		P Value
	Mean/ Median	SD/ IQR	Mean/ Median	SD/ IQR	
Maternal Age (years)	27.24	6.31	26.66	5.936	0.120
Gestational Age (weeks)	38.71	1.905	38.50	2.275	<0.001
Birth Weight (g)	3070.80	478.36	3048.84	551.835	0.082
Duration of stay	7.00	(0-89)	5.00	(0-65)	0.639
Discharge weight	3095.20	471.62	3043.59	566.056	<0.001

Discussion

This review highlights that perinatal asphyxia remains a substantial contributor to neonatal mortality for term neonates in South Africa. The overall survival rate of HIE was 85.0% with the majority that demised having had grade 3 HIE (see Table 3). No improvement has occurred in mortality and survival rate of HIE despite the introduction of IH as a treatment modality, this may be due to HIE 3's not being offered IH. The unchanged rates might be as a result of the small sample size of neonates that received IH. The incidence of HIE has increased, which could be better explained by the improvement in identifying HIE which is suggested by the improvement in assigning grades of HIE to neonates. The identification of HIE remains a challenging factor as in our setting there is lack of supporting equipment such as arterial blood gas ABG), aEEG or MRI , which hinders the diagnosis and in turn delays treatment as well as surveillance of HIE.

The 5-minute Apgar as a predictor of HIE remains complex. In this study, more than a quarter of neonates with Apgar of 5 and less, had no features of HIE, and a quarter of HIE neonates would be missed, as they had a 5-minute Apgar greater than 6. However, this study does highlight that an Apgar of less than 5 at 5-minutes and less than 7 at 10-minutes was a significant predictor of a poor outcome. These results are similar to those found by Bruckmann et al which is in a centre with similar resources as CMJAH. (3) Bruckmann et al and Horn et al both further emphasize the difficulty in isolating a criterion for HIE such as using either Apgar < 5 at 10 mins and/or ABG in 1st hour with severe metabolic acidosis and/or resus >10mins which each criteria have their defaults, which hinders the ability to record the incidence of HIE and set a benchmark from which improvement can be measured in South Africa. (3) (6)

In the current study, the presence of seizures, MAS, MSL, PPHN and grade 3 HIE which are markers of severe asphyxia, were all significant predictors of death. This emphasizes that maternal management and monitoring would play a vital role in improving outcomes for HIE. The increase in antenatal clinic attendance and emergency C/S does suggest that some improvement has occurred since the previous study. However, there is no improvement in survival rates which may suggest that the management is not appropriate or too late.

Shankaran et al's study reviewed whether longer (120 hours vs 72 hours) or deeper (32 degrees vs 33.5 degrees) IH could reduce mortality in an NICU setting. The study was aborted early due to safety concerns over cardiac arrhythmia, persistent acidosis, major vessel thrombosis and bleeding, and death. (12) These results have highlighted the importance of abiding to current IH protocol suggested of 72 hours and 33.5 degrees for moderate to severe HIE.

In the current study, the comparison between IH and non-IH yielded a significant difference in the grades which suggests the adherence of the CMJAH cooling protocol to perform IH for only moderate HIE's, grade 2 of Sarnat criteria. However, the HIE grade 3's that received IH, two thirds survived thus CMJAH should consider including HIE grade 3 to their IH criteria. There was also no significant increase in the common side effects of IH such as thrombocytopenia and sepsis. However, IH neonates had a significantly longer stay. This study highlights that IH had no significant increase in death and side effects and should be considered a viable safe treatment modality in LMIC's which have the same resources as CMJAH. A study to assess morbidity in developmental outcomes is required.

A recent review study reported that severe NNE neonates remain at high risk for death and morbidity despite IH (NNT 5 (95% CI 3, 25)), which accentuates the need for adjunctive neuroprotective therapies. (7) (12) Some neuroprotective therapies that are promising in preclinical trials but need further review are erythropoietin, xenon, melatonin, and stem cell therapies. Further studies exploring clinical management strategies in neonates with NNE are needed to improve outcomes, such as umbilical cord milking and sedative, anti-epileptics, and pressor medication. (13) These considerations may be a viable option in a resource constrained setting.

Study Limitations

This study's chief limitation is that it is retrospective and thus relies on medical notes of multiple doctors with various levels of experience. This limitation plays an important role in

identifying HIE with Apgar's, the clinical picture as well as assigning Sarnat grades and Thompson score. The study is also limited by the small sample size as it is a single centre based.

Conclusion

Perinatal asphyxia remains a major concern at CMJAH and worldwide as the consequences on neonatal mortality and morbidity are devastating. Asphyxia contributes greatly to neurodevelopmental delays and the cerebral palsy population which continue to put strain on an already overburdened health system. The introduction of IH for moderate HIE at CMJAH has not increased survival rates but a study would need to be conducted to assess the impact on the morbidity of HIE. The addition of IH for severe HIE and possible adjunct therapies should be considered and may impact the survival rate. The crude use of an Apgar less than 7 at 10-minutes could be used as a poor prognostic factor in resource limited areas where blood gases, a-EEG and MRI are unavailable. The identification of a set criteria to define HIE in LMIC settings is paramount to enable the incidence of HIE to be recorded and set a benchmark to improve the incidence in South Africa.

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Chapter 2 – Approved protocol

A REVIEW OF NEONATAL OUTCOMES TO DISCHARGE, OF PERINATAL ASPHYXIA AND THE USE OF INDUCED HYPOTHERMIA AS A TREATMENT MODALITY, AT A TERTIARY CENTRE IN SOUTH AFRICA

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Introduction

Background

Every year, perinatal and neonatal deaths account for 40% of the nine million deaths for children under 5 years of age. (14) Perinatal asphyxia accounts for 23% of those deaths, which highlights the global impact of this problem (14). Not only does perinatal asphyxia contribute to the high mortality rates but it also contributes greatly to the high morbidity rates, since those that survive may have serious neurological sequela ranging from developmental delay to severe cerebral palsy. (2,3,4)

Asphyxia is defined as any interruption in oxygen delivery, resulting in hypoxaemia, hypercapnia and metabolic acidosis. (3,4,5) Hypoxic ischemic encephalopathy (HIE) is a consequence of perinatal asphyxia and presents with neurological abnormalities on the first day of life. However once signs and symptoms of HIE are present, one has often missed the therapeutic window of opportunity for induced hypothermia. This emphasizes the importance of diagnosis and grading of HIE which is often not easily performed. One of the difficulties with diagnosing HIE in our population, is that one needs to identify a sentinel event, which is not always evident and often missed.

A consensus statement suggested by The American College of Obstetricians and Gynaecology and endorsed by the American College of Paediatrics aims to identify neonates with possible encephalopathy. The consensus defined neonatal encephalopathy as any infant born beyond 35 weeks of gestation presented with a subnormal level of consciousness or seizures; any presence of difficulty initiating or maintaining respiration and depression of tone and reflexes. This was further enhanced by a criteria used to diagnose neonatal encephalopathy which includes: An Apgar score of less than five at 5 and 10 minutes; fetal umbilical artery pH less than 7.0 or base deficit greater than or equal to 12; neuro-imaging evidence of acute brain injury consistent with HIE and lastly the presence of multisystem organ failure consistent with HIE. (15) Using these criteria will help to identify candidates for induced hypothermia intervention early and within the six-hour therapeutic window period.

A previous study at CMJAH assessing the outcomes of perinatal asphyxia during the period of 1 January 2006 to 31 December 2011, revealed an incidence of perinatal asphyxia of 4.7/1000 live births, as well as an overall survival rate of 86.7%. (4) Follow up records were poor with only 113 of 390 infants in the study attended follow up. (4) Those patients that had follow-up, 90 of 113 patients had normal development. (4) This is contrast to the study performed at Chris Hani Baragwanath Hospital (CHB) in 2011 with an incidence of asphyxia 8.7 to 15.2 per 1000 live births, with a mortality rate of 7.58%. (3) These studies highlight that perinatal asphyxia is a common cause of death in neonates in South Africa.

It has been established that HIE at a cellular level occurs in two phases following a reversible hypoxic ischaemic global insult. Phase one is the primary neuronal death due to cellular hypoxia with depletion of the cell's high-energy stores known as primary energy failure. (7)Phase two, is expected to occur six hours later from the initial insult, is known as delayed neuronal death. (7) The mechanisms involved in delayed neuronal death is characterised by initiation of apoptosis and mitochondrial dysfunction. (7) It is hypothesized that the second phase is associated with encephalopathy and increased seizure activity, and accounts for a significant proportion of the final cell loss which results in the severe morbidity and mortality of HIE. (7) This has resulted in a therapeutic window period of six hours in which induced hypothermia has shown to reduce the devastating effects of the delayed neuronal death phase resulting in improved mortality and morbidity outcomes.

The therapeutic hypothermia aims to lower the temperature of the vulnerable brain structures for example the basal ganglia, to 32 - 34 degrees Celsius. Two methods have been shown to be effective in newborn infants with HIE. These methods are whole body cooling and selective head cooling with mild systemic hypothermia. (16) (17) (18)

In a Cochrane Review of induced hypothermia in 2013, eight randomised controlled trials were included, containing 638 term infants with moderate to severe encephalopathy and evidence of intrapartum asphyxia. Therapeutic hypothermia resulted in a statistically significant and clinically important reduction in the combined outcome of mortality or major neurodevelopmental disability to 18 months of age. (16) Some side effects were noted such as an increase in the requirements for inotropic support of borderline significance and a

significant increase in thrombocytopenia. However, the review concluded that hypothermia's benefits far outweighed the risks of the adverse side effects. (5) (16)

With asphyxia, they often may require respiratory support in a neonatal intensive care unit (NICU). In South Africa, where resources are limited, there is competition for NICU beds. The result of this is that resources are offered to infants who are more likely to survive with minimal morbidity. With dismal mortality and morbidity rates of perinatal asphyxia, this often resulted in denial of NICU admission. (19) However, with the recent intervention of induced hypothermia, this may be challenged. This is further emphasized in Padayachee's study at CMJAH which showed those patients that gained access to NICU had a survival rate of 88.1% percent. (4)

One needs to consider if therapeutic hypothermia is a viable option in a developing country with low resources settings with limited access to NICU, low budget for expensive cooling machinery, amplitude EEG, and lack of trained health-care staff. A study performed at Tygerberg Children's hospital (TH), a tertiary centre in South Africa, revealed it was a feasible option in low resource settings and replicated similar results in reduction in mortality and morbidity as developed countries, however it requires a strict protocol and training of health care staff. (20) TH also used the Tecitherm TSmed 200 N system which is an expensive cooling machine which may not be available in many developing country health centres. (8)

A systematic review and meta-analysis of therapeutic hypothermia for neonatal encephalopathy in low and middle income countries was performed, which assessed the use of low cost cooling devices such as frozen gel packs and water bottles. This review showed that there was no statistically significant reduction in neonatal mortality, and even more alarming in the low-income country trial a five times higher mortality rate in cooled patients compared to those that received standard treatment, was reported. (8) Even though this review questions whether therapeutic hypothermia should be offered in low and middle income countries one should consider that these results could be due to the low technology devices and the lack of intensive nursing monitoring resulting in fluctuations in temperature which is potentially dangerous and non-neuroprotective. (5) (9)

A study done by Horn et al, was abruptly stopped as the cooling technique of selective head cooling with use of a solid ice cap resulted in large variations in temperature and showed difficult in maintaining systemic temperature above 35 – 35.5 °C. (17) This study highlights the need to assess the use of low technology devices and methods of cooling and, which would be appropriate and effective to function in a low resource setting. (17)

These studies highlight the necessity to evaluate each centre individually to whether therapeutic hypothermia is achieving comparable outcomes to high income countries, even when NICU facilities are not often available or provided to HIE neonates. Prior to offering therapeutic hypothermia there should be a strict requirement of the equipment, the training of health care providers and a strict protocol to the cooling requirements and procedure. (5) (20) (21) This study will be a retrospective descriptive review of neonatal encephalopathy, the rate of HIE, as well as the rate of HIE patients cooled and the possible side effects that were experienced. This study will also compare the results to previous rates obtained in Padachyee's et al study. This study may be useful in determining whether therapeutic hypothermia is viable treatment option in a low to middle income country for HIE.

Aim

To review the neonatal clinical and demographic characteristics and outcomes of perinatal asphyxia with induced hypothermia as a treatment modality in Charlotte Maxeke Johannesburg Academic Hospital.

Study Objectives

1. To describe the clinical and demographic characteristics of neonatal encephalopathy at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). These characteristics include: gender, mode of delivery, place of delivery, gestation, maternal age and parity, attendance to antenatal clinic, APGARS at 1, 5 and 10 mins, resuscitation requirements, HIE assessment, length of hospital stay and outcome to discharge.
2. To determine the rate of HIE and classify them into grades by the Sarnat Sarnat criteria. (appendix 2)

3. To determine the rate of therapeutic hypothermia and the side effects that were experienced.
4. To compare the prevalence, mortality, duration of hospital stay and grading of HIE of this study with Padchyee's study.

Methods

a. Study Design

This will be a retrospective descriptive study, reviewing an existing database of all neonates admitted at CMJAH from the 1 January 2013 to 31 July 2017 with the diagnosis of neonatal encephalopathy.

b. Sample Population

The Sample population includes all neonates admitted at CMJAH within the study period.

i. Inclusion Criteria

Neonates will be included in the sample if their birth weight was greater than 1800g, their 5-minute Apgar score of 5 and less and any evidence of neonatal encephalopathy.

ii. Exclusion Criteria

Neonates with possible causes of low Apgar scores other than perinatal asphyxia such as chromosomal abnormalities, obvious congenital abnormalities and any conditions incompatible with life will be excluded.

c. Data Collection

Patient information will be obtained from the existing computerized neonatal database at CMJAH. The data is compiled using Research Electronic Data Capture (REDCap) which is a secure web-based program that has been designed to assist in the collection of data for clinical audits. Standard information is collected by the attending medical staff prospectively and entered into the database with several verifications performed at different stages. The information included was demographic data, maternal information, Apgar scores at 1, 5 and 10 minutes, place of delivery, mode of delivery, birth weight, gestational age, need for ventilation after initial resuscitation, presence of seizures, grade of HIE, duration of hospital stay, cerebral cooling and side effects experienced, presence of meconium aspiration syndrome (MAS), persistent pulmonary hypertension and presence of confirmed

early or late neonatal sepsis. All this information will be used to complete the prepared data sheet for this study. (Appendix A). The Sarnat, Sarnat table is used in CMJAH neonatal unit to grade HIE. (Appendix B)

d. Data Analysis

Data will be analyzed using standard statistical methods with the use of statistical software SPSS. Continuous variables will be compared using unpaired t tests or Mann Whitney U analysis as appropriate depending on the distribution of data. The data of patient demographics and outcome variables will be compiled using descriptive study methods and expressed as means or medians for continuous variables. Categorical Variables will be compared using a Chi Square analysis and will be expressed as frequencies and percentages.

Ethics

The proposal of this study will be reviewed by the Ethical Committee for research on Human Subjects of the University of the Witwatersrand. The study will not commence until ethical clearance is obtained from the committee.

Timing

Task	2016				2017								
	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	June	Jul	Aug	Sept
Literature review													
Preparing protocol													
Protocol assessment													
Ethics application													
Collecting data													
Data Analysis													
Writing up- thesis													
Writing up - paper													

Figure 2- Gant chart depicting the timeframe proposed for this study

Funding

This is a retrospective study and will require the use of a well-established computerized neonatal database. Therefore, the cost involved will be for printing and stationery which will be covered by the investigator with an estimated budget of R2500.

Problems

This will be a retrospective study and data will be obtained from an already existing database which is reliant on the data captured from the attending staff during that period, this leads to concerns of inaccuracy and possible inadequate data. The identification and grading of HIE is not always efficiently done in prior studies and this may be due to the lack of a clear definition of HIE. (22)

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Appendix

a) Appendix 1 – Data Capture Sheet

Study Number		**Length of hospital stay**						
Demographics								
Gender	Male		Female		Unknown			
Mode of Delievery	NVD		Breech NVD		Assisted NVD			
	C/section	emergency		elective		Indication		
Place of Delivery	Inborn		Outborn		BBA			
Gestation								
Mat Age		**Parity**		**Gravity**				
ANC	Yes		No					
Delivery Room								
Apgars	1 min		5 Min		10 min			
Birth Weight		**Length**		**HC**				
Resus Required	None		Oxygen		BMV		Intubation	
Chest Compressions	Yes		No					
Adrenalin	Yes		No					
ABG	pH		pCO2		p02			
HCO3		BE						
HIE Assessment								
HIE	yes		no					
HIE Grading	I		II		III		Unknown	
Seizures	Yes		No					
MSL	Yes		No					
PPHN	Yes		No					
Icu admission	Yes		No					
IPPV	Yes		No					
Cooling	Yes		No					
Time of cooling		**Duration**			**Reason**			
Any side effects during cooling								
Thrombocytopenia	Yes		No					
Positive Blood Culture	Yes		No		INR			
Need for inotropes	Yes		No		Culture Result			
Need for respiratory support	Np02		NCPAP		IPPV			
Outcome	Discharge		Death		Length of hospital stay			

b) Appendix 2 – Sarnat Sarnat Modified Table

	Stage 1	Stage 2	Stage 3
Level of consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong, low threshold	Weak, incomplete, high threshold	Absent
Oculo vestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic function	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable, often unequal, poor light reflex
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased, diarrhoea	Variable
Seizures	None	Common, focal or multifocal	Uncommon (excluding decerebration)
Electroencephalogram findings	Normal (awake)	**Early:** low-voltage continuous delta and theta **Later:** periodic pattern (awake) Seizures: focal 1-to 1-Hz spike-and-wave	**Early:** periodic pattern with Isopotential phases **Later:** totally isopotential
Duration	Less than 24 hours	2 – 14 days	Hours to weeks

Chapter 3 - Appendix

a) Author Guidelines

Author Guidelines

Author Guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

To submit a manuscript, please proceed to the *SAJCH* Editorial Manager website: Editorial Manager

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Author contributions should be listed/described in the manuscript.

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Research ethics committee approval

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- Manuscripts must be written in UK English (this includes spelling).
- The manuscript must be in Microsoft Word or RTF document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

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- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

** NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

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- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions

- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research

Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

- May include up to 6 illustrations or tables.
- A max of 20 - 25references

Structured abstract

- This should be no more than 250words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
  - Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors. It should be able to be intelligible to the reader without referral to the main body of the article.
  - Do not include any references in the abstracts.

Here is an example of a good abstract.

***Scientific letters*/short reports**

These include case reports, side effects of drugs and brief or negative research findings.

Guideline word limit: 1500 words

- Abstract: unstructured, of about 100-150 words
- May include only one illustration or table
- A maximum of 6 references

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

Review articles

Review articlesshould always be discussed with the Editor prior to submission.

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners. They should be aligned to practice in South and/or sub-Saharan Africa and not a precis of reviews published in the international literature

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 400 words

Letters to the editor should relate either to a paper or article published by the SAJCH or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table

- Must include a correspondence address.

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide evidence of consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author.
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:

Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting..*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
  - On the Crossref homepage, paste the article title into the 'Metadata search' box.
  - Look for the correct, matching article in the list of results.
  - Click Actions > Cite
  - Alongside 'url =' copy the URL between { }.
  - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx/doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
- Government Gazettes:

  National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

  In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

  South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

  South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

  South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

  South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

  Rex v Jopp and Another 1949 (4) SA 11 (N)
  Rex v Jopp and Another: Name of the parties concerned
  1949: Date of decision (or when the case was heard)
  (4): Volume number
  SA: SA Law Reports
  11: Page or section number
  (N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.
  NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

b) Ethics clearance certificate

R14/49 Dr Rebecca Claire Simpson

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170116

NAME: (Principal Investigator)	Dr Rebecca Claire Simpson
DEPARTMENT:	Paediatrics and Child Health Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A Review of Neonatal Outcomes to Discharge, of Perinatal Asphyxia and the Use of Induced Hypothermia as a Treatment Modality, at a Tertiary Centre in South Africa
DATE CONSIDERED:	27/01/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Daynia Ballot and Dr David Rakotsoane
APPROVED BY:	Professor P. Cleaton-Jones,Chairperson, HREC (Medical)
DATE OF APPROVAL:	29/03/2017

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 in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised 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 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 review in January and will therefore be due in the month of January each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 3/04/17

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

c) Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Rebecca Claire Simpson (Student number: 0605148V) am a student registered for the degree of Mmed Paed S in the academic year 3rd.

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:  Date: 24/7/2018

d) Turn it in report

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