

https://dspace.org/

outcomes of neonates with perinatal asphyxia at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from 2007-2011

Padayachee, Natasha

2015-03-27
http://hdl.handle.net/10539/17341

Downloaded from a DSpace repository. https://dspace.org/

OUTCOMES OF NEONATES WITH PERINATAL ASPHYXIA AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL(CMJAH) FROM 2007 – 2011

Natasha Padayachee

695437

Degree of Master of Medicine in Paediatrics

A Research Report submitted to the Faculty of Science, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Medicine in Paediatrics.

8 May 2014

Declaration

I hereby declare that this research paper 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.

_____

Dr N Padayachee

_____day of_____20_____in_____

Abstract

Background: Perinatal asphyxia is a significant cause of death and disability.

Aim: To determine the outcomes (survival to discharge and morbidity post discharge) of neonates with perinatal asphyxia at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

Methods: This was a descriptive retrospective study. Patient information was obtained from the computerised neonatal database of neonates admitted to CMJAH within 24 hours of birth between 1 January 2006 and 31 December 2011 with a birth weight of >1800 grams and a 5 minute Apgar score <6.

Results: 450 babies were included in the study; 185 females (41.1%). Mean birth weight was 3034.80 grams (SD 484.936) and mean gestational age was 39.11 weeks (SD 2.2).

Most babies were inborn 391/450 (86.9%) and most were delivered by normal vaginal delivery 270/450 (60%). The overall survival was 390/450 (86.6%).

There were 42 babies admitted to ICU. The ICU survival was 37/42 (88.1%). Significant predictors of survival were place of birth (p value 0.006), mode of delivery (p value 0.007) and bag mask ventilation at birth (p value 0.040). The duration of stay (p value 0.000) was significantly longer in survivors (6.49 days SD 6.6). The remaining factors were not significantly different between the two groups.

The rate of perinatal asphyxia (Apgar score <6) was 4.68 per 1000 live births; while 3.61 per 1000 live births had evidence of hypoxic ischaemic encephalopathy (HIE).

Of the 390 babies discharged from CMJAH, 113 had follow up records (28.97%) to a mean corrected age of 5.88 months (SD 5.03). The majority (90/113 – 79.64%) had normal development.

Conclusion: i) The high overall survival and survival after ICU admission provides a benchmark for further care. ii) Obtaining adequate data for long term follow up was not possible with the existing resources and surrogate early markers of outcome and / or more resources to ensure accurate follow-up are needed and iii) the high incidence of

HIE suggest that a therapeutic hypothermia service including long-term follow-up component would be beneficial.

Acknowledgements

I would like to thank my supervisor, Professor D E Ballot for her continuous support, guidance and encouragement. Prof Ballot has provided immense inspiration and inculcated an appreciation for research and improvement.

I would like to thank Professor D F Wittenberg for his interest in my research and accepting it for publication.

I would also like to thank my husband, Judian Govender, friends and family and God, who made all things possible.

Table of Contents

Declaration....1
Abstract....2
Acknowledgements....4
List of Tables....6
Nomenclature (Abbreviations)....7
Chapter One....8
Introduction....8
Scope of the problem....8
Diagnosis of Perinatal Asphyxia....10
Hypoxic ischaemic encephalopathy....10
Justification for the current study....14
Aim....14
Chapter Two....15
Subjects and Methods....15
Statistical Analysis....17
Chapter 3....18
Results....18
ICU admissions....21
Mortality....21
Comparison between survivors and non survivors....21
Follow Up....24
Chapter 4....25
Discussion and Conclusion....25
Limitations....26
Conclusion....27
References....28
Article Reprint....31
Ethics Clearance....37

List of Tables

Sarnat and Sarnat stages of Hypoxic-Ischaemic Encephalopathy……12

Table 1: Clinical and demographic Characteristics……..…19

Table 2: Problems in pregnancy……..20

Table 3: Univariant analysis for determinants of survival.....……22

Table 4: Comparison between survivors and non-survivors for continuous variables…23

Table 5: Neonatal follow up results…….24

Nomenclature (Abbreviations)

CMJAH - Charlotte Maxeke Johannesburg Academic Hospital

CO_2 - Carbon dioxide

HIE - Hypoxic Ischaemic Encephalopathy

PPIP - Perinatal Problem Identification Programme

SAPA - South African Paediatric Association

CK-BB - creatine kinase brain bound

MRI - magnetic resonance imaging

CT - computed tomography

BBA - Born Before Arrival

aEEG - amplitude-integrated electroencephalography

MAS - Meconium Aspiration Syndrome

PPHN - Persistent Pulmonary Hypertension of the newborn

NNFU - Neonatal follow up clinic

NICU - Neonatal Intensive Care Unit

Chapter One

Introduction

Asphyxia is defined as any perinatal insult resulting in suffocation with anoxia and increased carbon dioxide (CO_2).[1] Severe hypoxia or ischemia of the fetus can manifest in the newborn as an encephalopathy and may result in neonatal death or in permanent motor and mental handicap.[1-3]

The outcomes of Hypoxic Ischaemic Encephalopathy (HIE) vary between death and intact survival.[4] There is a spectrum of long term morbidity in survivors that ranges from mild motor and cognitive abnormalities to cerebral palsy and severe deficits.[3-6] The prognosis for those infants who survive very severe perinatal asphyxia is difficult to judge.[7, 8]

Scope of the problem

Perinatal asphyxia is an important health issue on a global scale. Over nine- million children die every year during the perinatal and neonatal periods and nearly all (98%) of these deaths occur in developing countries Every year approximately 4 million babies are born asphyxiated; this results in 1 million deaths and an equal number of serious neurological consequences ranging from cerebral palsy, mental retardation and epilepsy.[9-11] It is a major contributing factor in perinatal and neonatal mortality which indicates social, educational and economical standards of a community.

Neonatal deaths account for almost 40% of under five deaths, so it is apparent that Millennium Developmental Goal 4 (aiming at a two thirds reduction in under-five mortality by the year 2015 from a base line in 1990) can only be met by substantially reducing neonatal deaths.[10] Perinatal asphyxia is the fifth largest cause of under 5 deaths (8.5%) after pneumonia, diarrhoea, neonatal infections and complications of preterm birth.[10, 12]

Perinatal asphyxia in South Africa

The death of an infant as a result of perinatal asphyxia is devastating and frequently avoidable. In developed countries which have well-functioning health services these deaths are a rare occurrence and prevention is widely understood. However, perinatal audit using Perinatal Problem Identification Programme (PIPP) has identified perinatal asphyxia as a common and important cause of death in certain areas of South Africa.[13,14] At Chris Hani Baragwanath hospital, 20% of all neonatal deaths are due to asphyxia.[15] Wild studied a group of 25 term asphyxiated infants admitted to Johannesburg Hospital Neonatal Unit between September 1980 and March 1982.[16] The mortality was 20%, and 16% were handicapped at the 2 year assessment. Twenty percent of patients were lost to follow up. Scher had undertaken a follow up to this study. In Scher's retrospective study of 109 term infants with moderate to severe birth asphyxia there was a poor prognosis particularly in patients with seizures and cardiopulmonary signs of asphyxia, but also if multi-organ dysfunction was taken into account.[17]

The fundamental goal of establishing perinatal audits in areas with high perinatal mortality rates is to reduce the number of perinatal deaths through an improvement in the quality of care. Several studies have shown a strong association between the establishment of an effective audit process and improvement of the quality of maternal health services and perinatal mortality rates.[14,18] Currently there are limited available data and despite the enormous magnitude, available figures are likely to underestimate the real problem.[12]

Until recently, solving the problem of perinatal asphyxia lay mainly in the obstetric realm. Prompt and effective neonatal resuscitation can improve outcome. This has been addressed by the development and implementation of the South African Neonatal Resuscitation programme[19] endorsed by the South African Paediatric Association (SAPA).

Diagnosis of Perinatal Asphyxia

The major difficulty in collecting accurate epidemiological data is a lack of a common definition of the diagnosis criteria of the condition.[10] Umbilical artery pH that defines asphyxia of a sufficient degree to cause brain injury is unknown. Although the most widely accepted definition is a pH <7.0, even with this degree of acidosis the likelihood of brain injury is low.[20, 21]

The means of assessment include testing umbilical pH, 1 hour post- delivery blood gas, low Apgar scores, neurological changes ranging from twitching to hypotonia and seizures. Given the lack of resources in developing countries, perinatal asphyxia can be crudely assessed by use of the Apgar score.[12] Apgars at 10 minutes provide useful prognostic data before other evaluations are available for infants. Low Apgar scores at 1, 5 and 10 minutes were markers of increased risk of death or chronic motor disability.[22-25] More scientific methods have been used, however in resource deplete settings, this is not possible.[2]

Hypoxic ischaemic encephalopathy

Neonatal depression is a general term used to describe an infant who has a prolonged transition from an intrauterine to an extra-uterine environment. These infants usually have low 1- and 5-minute Apgar scores.[24] Neonatal encephalopathy is a clinical term used to describe an abnormal neurobehavioral state that consists of a decreased level of consciousness with abnormalities in neuromotor tone. It characteristically begins within the first postnatal day and may be associated with seizure-like activity, hypoventilation or apnoea, depressed primitive reflexes and the appearance of brain stem reflexes. It does not imply a specific aetiology, nor does it imply irreversible neurologic injury.

Hypoxic-ischemic encephalopathy (HIE) is an abnormal neurobehavioral state in which the predominant pathogenic mechanism is impaired cerebral blood flow. Hypoxic-ischemic brain injury refers to neuropathology attributable to hypoxia and/or ischemia as evidenced by biochemical (such as serum creatine kinase brain bound [CK-BB]), electrophysiologic (EEG), neuroimaging (head ultrasonography [HUS], magnetic resonance imaging [MRI], computed tomography [CT]), or post-mortem abnormalities.[12, 21]

The problem of benchmarking definitions of HIE in the South African context has been specifically discussed in a 2012 publication. Horn et al. showed that there is wide variation in the incidence and grade of HIE, depending on which criteria are used.[26]

The diagnosis of perinatal HIE requires an abnormal neurologic examination on the first day following birth. The clinical spectrum of HIE is described as mild, moderate and severe according to the Sarnat Stages of HIE.[4, 27] Infants can progress from mild to moderate and/or severe encephalopathy over the 72 hours following the hypoxic-ischemic insult.[6, 28]

Sarnat and Sarnat Stages of Hypoxic-Ischemic Encephalopathy*

Stage	**Stage 1 (Mild)**	**Stage 2 (Moderate)**	**Stage 3 (Severe)**
Level of consciousness	Hyper alert; irritable	Lethargic or obtunded	Stuporous, comatose
Neuromuscular control:	Uninhibited, overreactive	Diminished spontaneous movement	Diminished or absent spontaneous movement
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive, disinhibited	Decreased or absent
Segmental myoclonus	Present or absent	Present	Absent
Complex reflexes:	Normal	Suppressed	Absent
Suck	Weak	Weak or absent	Absent
Moro	Strong, low threshold	Weak, incomplete high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic function:	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Midposition, often unequal; poor light reflex
Respirations	Spontaneous	Spontaneous; occasional apnea	Periodic; apnea
Heart rate	Tachycardia	Bradycardia	Variable

Bronchial and salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased diarrhea	Variable
Seizures	None	Common focal or multifocal (6 to 24 hours of age)	Uncommon (excluding decerebration)
Electroencephalographic findings	Normal (awake)	Early: generalized low-voltage, slowing (continuous delta and theta)	Early: periodic pattern with isopotential phases
		Later: periodic pattern (awake); seizures focal or multifocal; 1.0 to 1.5 Hz spike and wave	Later: totally isopotential
Duration of symptoms	<24 hours	2 to 14 days	Hours to weeks
Outcome	About 100% normal	80% normal; abnormal if symptoms more than 5 to 7 days	About 50% die; remainder with severe sequelae

* The stages in this table are a continuum reflecting the spectrum of clinical states of infants over 36 weeks' gestational age.

Source: From Sarnat H. B., Sarnat M. S. Neonatal encephalopathy following fetal distress: A clinical and electroencephalographics study. *Arch Neurol* 1976;33:696.

Justification for the current study

Perinatal asphyxia is an important problem in developing country communities, accounting for more deaths then measles or malaria, yet receiving much less policy and programmatic attention.[10] The value of regular perinatal audit may identify suboptimal care related to perinatal deaths and thus appropriate measures for its reduction.[18] The consequences experienced by survivors of perinatal asphyxia results in an increased economic and social burden on families and the community. This impact in predominately experienced in resource depleted developing countries. Interventions to reduce disability are warranted.

There is a need for current information to determine the need and use of cerebral cooling. There is evidence that induced hypothermia (cooling) of newborn babies who may have suffered from a lack of oxygen at birth reduces death or disability, without increasing disability in survivors. The benefits of cooling on survival outweigh the short term adverse effects.[29, 30] Studies such as the NICHD, CoolCap trials and TOBY have shown that hypothermia works and should be offered to all term and near term babies with moderate or severe neonatal encephalopathy. This therapy should no longer be considered investigational.[29, 31-33]

Aim

The aim of this study is to determine the outcomes in terms of survival to discharge and morbidity post discharge of neonates with perinatal asphyxia at Charlotte Maxeke Johannesburg Hospital (CMJAH).

Chapter Two

Subjects and Methods

This was a descriptive retrospective study. The study population included all neonates delivered at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from 1 January 2006 to 31 December 2011. Babies who were born before arrival (BBA) and neonates transferred from other hospitals were included if arrival at CMJAH within 24 hours of birth. The total live births estimated from CMJAH and the two major midwife obstetric units affiliated to the hospital are 1310 per month (delivery figures are for 2011).

Babies were included in the sample if the birth weight was greater than 1800g and the 5 minute Apgar score was less than 6. Sarnat and Sarnat classification was used for grading of HIE. Depending on neurobehavioural signs neonates were divided into three stages 1, 2 and 3. According to the classification stages 1, 2, and 3 correlates with the description of mild, moderate and severe encephalopathy respectively.[34] Not all babies had a grade of HIE assigned to them. The recorded discharge diagnoses were reviewed and those with other evidence of possible encephalopathy (poor suck, lethargy, seizures, decreased tone or lack of responsiveness) recorded on discharge diagnosis was also noted. These babies were presumed to have HIE however they could not be graded retrospectively

Babies with possible causes of a low Apgar scores other than perinatal asphyxia such as chromosomal abnormalities, obvious congenital abnormalities of the central nervous system, spinal muscular atrophy, and conditions incompatible with life were excluded.[17] Babies who had meconium aspiration or who were subsequently proven to have neonatal sepsis were included in the study.

All attending staff received training according to the South African Paediatric Association (SAPA) guidelines in order to start appropriate resuscitation immediately.[19] Babies with HIE grade 2-3 were not routinely ventilated as per the discretion of the attending physician because of resource constraints, resulting in limited availability of Neonatal Intensive Care Unit beds and ventilators. These babies received all other care

including supplemental oxygen, fluids, anticonvulsants, nutrition and antibiotics as required. Cerebral cooling was only started at the end of the study period and done in ICU. Magnetic Resonance Imaging (MRI) was not available during the study period.

Patient information was obtained from the computerised neonatal database. The neonatal database at CMJAH is kept for purposes of clinical audit. Standard information is collected prospectively by attending medical house staff and entered into a Microsoft Access programme by a data capturer. This included 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, mortality, duration of hospital stay, cerebral cooling and aEEG findings, presence of meconium aspiration syndrome (MAS), persistent pulmonary hypertension of the newborn (PPHN), and presence of neonatal sepsis. Only culture proven sepsis, both early (<72hours) and late (>72 hours) were considered. The neonatal unit submits mortality data to the PIPP database (www.pipp.co.za). The final PIPP diagnosis was reviewed for all deaths.

There is a routine post discharge neonatal follow up clinic (NNFU). This is staffed by Paediatricians, Medical Officers, Occupational Therapists, Physiotherapists and Speech Therapists. Patients are given a clinic appointment on discharge. Defaulters are contacted once in writing, no further attempt is made to ensure follow up. Follow up visits are recorded and stored in the clinic files.

NNFU records were reviewed. The noted findings of the attending doctor and the multidisciplinary team were recorded. Outcome at follow up was recorded as normal neurological development (age appropriate milestones achieved, normal vision and hearing), cerebral palsy, and developmental delay, and microcephaly, cortical blindness, hearing loss or seizures. The outcome was noted at the last clinic attendance for each patient.

Statistical Analysis

Data was entered onto an MS-Excel spread sheet and then imported to the statistical software SPSS version 20 IBM ™ for analysis. Data was analysed in terms of standard statistical methods. The analysis of patient demographics and baseline outcome variables were summarised using descriptive study methods: expressed as mean (standard deviation) or median (range) for continuous variables and frequency and percent for categorical variables. Survivors and non survivors were compared. Categorical data were compared using chi-square analysis and continuous data using unpaired T-Tests (as the distribution was normal).

Chapter 3

Results

A total of 470 babies were eligible for inclusion into the study; however 7 babies were excluded as there was no clinical data available at all and 13 babies were excluded due to presence of major congenital abnormalities. The final sample thus consisted of a total of 450 babies; 185 females (41.1%) and 260 males (57.8%). The mean maternal age was 25.63 years (SD 6.1) and the maternal parity was 1 (IQR 1-9). The birth weight ranged from 1800 – 4596 grams with a mean 3034.80 grams (SD 484.93) and a mean gestational age of 39.11 weeks (SD 2.2). Clinical and demographic characteristics are shown in Table 1.

The majority of babies were inborn 391/450 (86.9%) and most were delivered by normal vaginal delivery 270/360 (60%). Problems in pregnancy were documented in 228/450 (50.66%) of cases (See Table 2) - fetal distress being the most common 91/450 (20.2%).

A total of 346 (77.1%) of babies had evidence of HIE but only 158 (45.5%) of these had a grade of HIE. The rate of perinatal asphyxia (Apgar score <6) was 4.68 per 1000 live births; while that of babies with evidence of HIE was 3.61 per 1000 live births.

Table 1: Clinical and demographic characteristics

Characteristic		**Total 450**
Maternal age (years)		Mean 25.63 (SD 6.1)
Parity		Median 1 (IQR 1-9)
Antenatal Care	Yes	306 (68.0%)
	No	73 (16.2%)
	Not recorded	71 (15.8%)
Place of delivery	Inborn	391 (86.9%)
	Outborn	48 (10.7%)
	Born Before Arrival	11 (2.4%)
Mode of Delivery	NVD	270 (60%)
	C/S emergency	120 (26.7%)
	C/S elective	19 (4.2%)
	Vaginal Breech	9 (2.0%)
	Assisted vaginal delivery	1 (0.2%)
	Not Recorded	31 (6.9%)
Gestational Age		Mean 39.11 (SD 2.2)
Birth Weight		Mean 3034.80 (SD 484.9)
Gender	Male	260 (57.8)
	Female	185 (41.1)
	Unknown	5 (1.1)
Apgar	1 minute Apgar	Median 3 (IQR 0-5)
	5 minute Apgar	Median 4 (IQR 1-5)
	10 minute Apgar	Median 6 (IQR 1-10)
Bag Mask Ventilation	Yes	334 (74.2%)
	No	116 (25.8%)
Chest compressions	No	406 (90.2%)
	Yes	44 (9.8%)
Presence of seizures	No	363 (80.7%)
	Yes	87 (19.3%)
Meconium Aspiration Syndrome	No	357 (79.3%)
	Yes	93 (20.7%)

Persistent Pulmonary Hypertension of the Newborn	No	448 (99.3%)
	Yes	3 (0.7%)
Culture positive sepsis *	No	437 (97.1%)
	Yes	13 (2.9%)
Babies with HIE**	Yes	347 (77.1%)
	No	103 (22.9%)
HIE grade	1	58 (12.9%)
	2	66 (14.7%)
	3	34 (7.6.0%)
ICU* Admission**	No	408 (90.7%)
	Yes	42 (9.3%)
Duration of hospital stay (days)		Median 4 (IQR 0-76)

*Early and Late

** Discharge diagnosis (see full text) HIE- Hypoxic Ischaemic Encephalopathy

*** Intensive Care Unit

Table 2: Problems in pregnancy

Problem	**Total = 450**
Fetal distress	91 (20.2%)
Meconium Stained Liquor	49 (10.9%)
Fetal distress & Meconium Stained Liquor (MSL)	39 (8.7%)
Multiple Problems	15 (3.3%)
Cord around the neck	14 (3.1%)
Prolonged second stage	9 (2.0%)
Cord Prolapse	4 (0.9%)
Poor Progress	4 (0.9%)
Malpresentation	1 (0.2%)
Cephalopelvic disproportion	1 (0.2%)
Shoulder dystocia	1(0.2%)

ICU admissions

There were 42 babies admitted to ICU, 15 babies were female and 27 male. Of the 42 babies admitted to ICU, 15 had Meconium Aspiration Syndrome (MAS) (35.7%), 9 had HMD (21.4%) and 3 had Persistent Pulmonary Hypertension of the Newborn (PPHN) (7.1%). The ICU survival was 37/42 (88.1%). There were two babies from the study who received cerebral cooling post perinatal asphyxia. They were monitored in NICU and both survived.

Mortality

The overall survival was 390/450 (86.7%). The causes of death according to the PIPP classification were as follows; perinatal asphyxia 53/60 (88.3%), meconium aspiration and perinatal asphyxia 3/60 (5.0%), hyaline membrane disease 1/60 (1.6%), group B streptococcal infection 2/60 (3.3%) and hypovoleamic shock 1/60 (1.6%). Significantly more babies who died had evidence of HIE (see Table 4)

Comparison between survivors and non survivors

Various factors were compared between the babies that survived and those that died (see Table 3 and 4). Place of birth (p value 0.006), mode of delivery (p value 0.007) and bag mask ventilation at birth (p value 0.040) were all significantly associated with survival. The duration of stay (p value 0.000) was significantly longer in survivors. The remaining factors were not significantly different between the two groups.

Table 3: Univariate analysis for determinants of survival

Characteristic	Survivors	Non- Survivors	Chi Square	P value
Gender			0.212[a]	0.899
Male	226/260 (86.9%)	34/260 (13.1%)		
Female	160/185 (86.5%)	25/185 (13.5%)		
Not recorded	4/5(80%)	1/5 (20%)		
Antenatal Care			2.731[a]	0.255
Yes	265/306 (86.6%)	41/306 (13.4%)		
No	60/73 (82.2%)	13/73 (17.8%)		
Not recorded	65/71 (91.5%)	6/71 (8.5%)		
Place of delivery			10.129[a]	0.006
Inborn	344/391 (88.0%)	47/391 (12%)		
Outborn	35/48 (72.9%)	13/48 (27.1%)		
BBA	11/11 (100%)	0/11 (0.0%)		
Mode of Delivery			15.888[a]	0.007
NVD	226/270 (83.7%)	44/270 (16.3%)		
C/S Emergency	106/120 (88.3%)	14/120 (11.7%)		
C/S Elective	19/19 (100%)	0/19 (0.0%)		
Vaginal Breech	9/9 (100%)	0/9 (0.0%)		
Assisted delivery	0/1 (0.0%)	1/1 (100%)		
Not recorded	30/31 (96.8%)	1/31 (3.2%)		
Bag Mask Ventilation			4.203[a]	0.040
Yes	283/334(84.7%)	51/334 (15.5%)		
No	107/116 (92.2%)	9/116 (7.8%)		
Chest compressions			3.724[a]	0.540
No	356/406 (87.7%)	50/406 (12.5%)		
Yes	34/44 (77.3%)	10/44 (22.7%)		
MAS*			1.724[a]	0.189
No	314/357 (88.0%)	43/357 (12.0%)		
Yes	77/93 (82.8%)	16/93 (17.2%)		

PPHN**			0.456[a]	0.500
No	388/447 (86.8%)	59/447 (13.2%)		
Yes	3/3 (100.0%)	0/3 (0.0%)		
Culture positive sepsis***			0.345[a]	0.557
No	379/437 (86.7%)	58/437 (13.3%)		
Yes	13/13 (92.3%)	1/13 (7.7%)		
Babies with HIE******			15.000[a]	0.000
No	101/103 (98.1)	2/103 (1.9%)		
Yes	289/347 (83.3%)	58/347 (16.7%)		
HIE Grade			61.389[a]	0.000
HIE 1	56/58 (96.6%)	2/58 (3.4%)		
HIE 2	53/66 (80.3%)	13/65 (19.7%)		
HIE 3	8/34 (23.5%)	26/34 (76.5%)		
Not recorded	273/292 (93.5%)	19/292 (6.5%)		
ICU******* Admission**			0.820[a]	0.775
No	353/408 (86.5)	55/408 (13.5%)		
Yes	37/42 (88.1%)	5/42 (11.9%)		

*MAS – Meconium Aspiration Syndrome

**PPHN – Persistent Pulmonary Hypertension of the Newborn

***Early and late

**** Discharge diagnosis (see full text) HIE – Hypoxic ischaemic Encephalopathy

*****ICU – Intensive Care Unit

Table 4: Comparison between survivors and non survivors for continuous variables

Characteristic	**Survivors**		**Non-survivors**		**P Value**
	Mean	SD	Mean	SD	
Maternal Age	25.61	6.097	26.22	6.804	0.579
Birth Weight	2895.68	589.064	2962.65	514.678	0.405
Gestational Age	38.07	2.943	38.62	2.293	0.175
Duration of hospital stay	6.49	6.6	2.82	9.766	0.000

Follow Up

Of the 390 babies discharged from CMJAH, 113 had follow up records (29%) to a mean corrected age of 5.88 months (SD 5.03). The majority (90/113 – 79.6%) had normal development. Details of the disability are shown in Table 5.

Table 5: Neonatal follow up results

Records available	
No	277/390 (71.0%)
Yes	113/390 (29.0%)
Normal development	90/113 (79.6%)
Cerebral palsy	13/113 (11.5%)
Developmental delay	6/113 (5.3%)
Microcephaly	1/113 (0.9%)
Cerebral palsy and microcephaly	2/113 (1.8%)
Developmental delay and microcephaly	1/113 (0.9%)
Seizures	1/113 (0.9%)

Chapter 4

Discussion and Conclusion

This review shows that perinatal asphyxia at CMJAH remains a common problem with approximately 6 admissions every month. In hospital mortality was low 60/450 (13.3%) with the burden anticipated to be in the disabled survivors. Our rate of perinatal asphyxia and HIE was similar to that found by Horn et al.[26]

The 5 minute Apgar score is a poor indication of cerebral injury. In this study, 103 (22.9%) of babies had no evidence of HIE, although 347 (77.1%) had signs of neurological compromise recorded. Attending staff do not routinely allocate a grade of HIE. Only 158 babies had a grade of HIE. This is a very important omission as it is difficult to decide retrospectively. Possible reasons for the lack of proper grading or a detailed neurological examination may be related to challenges in a busy resource constrained setting, lack of continuity of care as different health care workers review patients daily or health care workers are not adequately trained on the criteria to examine for and the grading to allocate.

There are few population-based studies of HIE in sub-Saharan Africa, and the published criteria that are used to define and grade HIE are too variable for meaningful comparisons between studies and populations. Horn et al discuss the difficulties in consensus definitions and criteria of HIE. The data show that there is a wide variation in the incidence and grade of HIE depending on which criteria is used.[26] A more refined method of classifying perinatal asphyxia than the 5 minute Apgar score is required, possibly TOBY[30] or CoolCap[29] definitions, however these require special investigations. There is a need to encourage staff to accurately assign an HIE grade. The need for resuscitation at birth predicted outcome and could be included in the definition of perinatal asphyxia in resource poor settings, where there is no arterial blood gas or amplitude electroencephalogram available.

There are increasing challenges in a busy resource constrained setting where only 74.2% of infants born with a 5-minute Apgar score less than 6 received bag mask resuscitation. Prior to implementing a cooling programme, it is essential to ensure adequate neonatal resuscitation and for strict HIE grading on all asphyxiated neonates.

Attendance at neonatal follow up is unacceptably low. Only 113/390 (29%) of babies had attended. The lack of follow up may be due to the low socio-economic status of the

population and the level of education of parents/guardians. It is possible that many asphyxiated babies may have demised after discharge or that disabled children are kept at home without access to health care. It was disappointing that the two babies who had received cerebral cooling did not present for follow up. It is therefore not possible to accurately report rates of post discharge disability or mortality. Of the 113 patients with follow up data, 24 (21.2%) had disability.

From the study results, the predictors of survival were mode of delivery, place of birth and resuscitation at birth. Elective caesarean delivery was associated with improved outcomes. Unexpectedly all babies delivered by vaginal breech survived. A study showed that for fetal breech presentation, neonatal outcome was better with planned caesarean section rather than vaginal breech.[35] In contrast a study from Europe showed that neonatal outcome from planned vaginal breech delivery was not different from elective caesarean section deliveries.[36] However, we do not know if our breech deliveries were planned. All babies born before arrival (BBA) survived. It is possible that those babies who were more severely asphyxiated may have demised at home or arrived dead at hospital. The data relating to that information was beyond the scope of this study. The duration of hospital stay was shorter for those who demised indicating that their condition was very severe and resulted in early death.

Limitations

This is a retrospective study which relies on data from attending staff with inaccuracies and loss of data. This study describes the incidence of perinatal asphyxia as defined by a 5 minute Apgar score less than 6, there is insufficient data to comment on the incidence of moderate-severe HIE and the incidence of morbidity after discharge. The lack of a clear definition of HIE was a further limitation. A prospective follow up of babies who sustain perinatal asphyxia is warranted.

Conclusion

The impact and burden of perinatal asphyxia is an immense problem worldwide, while efforts and resources should be aimed at prevention wherever possible. Perinatal asphyxia is a major cause of death and disability. The high overall survival and morbidity remains a significant problem. The need for a good resuscitation programme which emphasises early and timeous response is paramount. The value of good resuscitation efforts by skilled medical professionals with accurate documentation will assist in obtaining consensus definitions in our resource constrained environments.

The study confirms that perinatal asphyxia remains a significant problem at CMJAH, the high overall survival and morbidity and survival after ICU admission provides a benchmark for further care. There is a need for obtaining adequate data for long term follow up as this was not possible with the existing resources. Further research is required to establish consensus definitions that can be used for meaningful population studies and benchmarking of hypoxic ischaemic encephalopathy.

Perinatal asphyxia can trigger a cascade of neurotoxic events. The delay in onset of neuronal and glial injury has allowed for the potential benefits of neuro-protective interventions. The benefit of a cooling programme should no longer be considered as experimental research and its implementation may be warranted in our settings. More resources to ensure accurate follow-up are needed and the high incidence of HIE suggest that a therapeutic hypothermia service including a long-term follow-up component would be beneficial.

References

1. Freeman JM, Nelson KB. Intrapartum Asphyxia and Cerebral Palsy. Pediatrics. 1988;82(2):240-9.

2. Gregersen NE, Ballot DE, Guidozzi F, Cooper PA. Birth asphyxia, presenting a case for 'a stitch in time'. SAMJ. 1999;Vol. 89(March).

3. Begum Ha Fau - Rahman A, Rahman A Fau - Anowar S, Anowar S Fau - Mortuza A, Mortuza A Fau - Nahar N, Nahar N. Long term outcome of birth asphyxiated infants. (1022-4742 (Print)).

4. Perlman M Fau - Shah PS, Shah PS. Hypoxic-ischemic encephalopathy: challenges in outcome and prediction. (1097-6833 (Electronic)).

5. de Vries LS, Jongmans MJ. Long-term outcome after neonatal hypoxic-ischaemic encephalopathy. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2010;95(3):F220-F4.

6. Klein M Fau - Reynolds JL, Reynolds JL. Influence of perinatal asphyxia on neurologic outcome: consequences for family practice accoucheurs. (0008-350X (Print)).

7. Scott H. Outcome of very severe birth asphyxia. Archives of Disease in Childhood,. 1976;51(february):712-6.

8. Al-Macki N Fau - Miller SP, Miller Sp Fau - Hall N, Hall N Fau - Shevell M, Shevell M. The spectrum of abnormal neurologic outcomes subsequent to term intrapartum asphyxia. (1873-5150 (Electronic)).

9. Majeed R Fau - Memon Y, Memon Y Fau - Majeed, Farrukh, Majeed F Fau-Shaikh, Naheed Parveen, Shaikh Np Fau - Rajar, Uzma D. M.Rajar, U. D. Risk factors of birth asphyxia. (1025-9589).

10. Lawn JE, Manandhar A, Haws RA, Darmstadt GL. Reducing one million child deaths from birth asphyxia--a survey of health systems gaps and priorities. Health research policy and systems / BioMed Central. 2007;5:4. Epub 2007/05/18.

11. Nilufar Shireen NN, AH Mollah. Risk Factors and Short-Term Outcome of Birth Asphyxiated Babies in Dhaka Medical College Hospital. Bangladesh J Child Health. 2009;33 ((3)):83-9.

12. Dr Ornella Lincetto WG, Milano, . Birth Asphyxia - Summary of the previous meeting and protocol overview. WHO, 11June 2007.

13. Buchmann Ej Fau - Pattinson RC, Pattinson Rc Fau - Nyathikazi N, Nyathikazi N. Intrapartum-related birth asphyxia in South Africa--lessons from the first national perinatal care survey. (0256-9574 (Print)).

14. Ed RC Pattinson. Tshepesa Press. Saving Babies 2008-2009. The MRC Unit for Maternal and Infant Health Care Strategies, Klinikala Building, Kalafong Hospital, Private Bag 667, Pretoria, 0001: MRC Research Unit for Maternal and Infant Health Care Strategies, PPIP Users and the Saving Babies Technical Task Team, 2008-2009.

15. Cooper PA PK. Analysis of term asphyxiated infants at Baragwanath Hospital. Proceedings of the Eleventh Conference on Priorities in Perinatal Care in South Africa. 1992;Department of Paediatrics, University of Witwatersrand.

16. Wild C RA, Thompson PD, Cohn R. Outcome for Premature Infants versus Full Term Asphyxia Proceedings of the Third Conference on Priorities in Perinatal Care in South Africa. 1984;Department of Paediatrics, University of Witwatersrand.

17. Scher LG. Outcome following asphyxial insult in Term Neonates: Witwatersrand Johannesburg; 2000.

18. Kidanto HL, Mogren I, van Roosmalen J, Thomas AN, Massawe SN, Nystrom L, et al. Introduction of a qualitative perinatal audit at Muhimbili National Hospital, Dar es Salaam, Tanzania. BMC Pregnancy Childbirth. 2009;9:45. Epub 2009/09/22.

19. Prof Daynia Ballot DMU, Prof Miriam Adhikari, Prof Keith Bolton, Prof Peter Cooper, Dr Graham Ducasse, Prof Ashraf Coovadia, Prof Beyers Hoek, Prof Gert Kirsten, Prof Haroon Saloojee, Prof Sithembiso Velaphi, Prof Dave Woods, Prof Johan Smith, Dr Clarissa Pieper, Dr Alan Horn, Dr Gary Reubenson, Dr Hitesh Diar, Dr Firdose Nakwa, Dr Elizabeth Ho. South African Handbook of Rescusitation of the Newborn. Association SAP, editor2004.

20. Thornberg E Fau - Thiringer KTKF-O, A. Odeback A Fau-Milsom, I. Milsom. Birth asphyxia: incidence, clinical course and outcome in a Swedish population. (0803-5253).

21. John P Coherty ECE, Ann R Stark. Manual of Neonatal Care, 6th edition2008.

22. Ellenberg KBNaJH. Apgar scores as predictors of chronic neurologic disability. Pediatrics. 1981;68(36):36-44. Epub 44.

23. Laptook AR, Shankaran S, Ambalavanan N, Carlo WA, McDonald SA, Higgins RD, et al. Outcome of Term Infants Using Apgar Scores at 10 Minutes Following Hypoxic-Ischemic Encephalopathy. Pediatrics. 2009;124(6):1619-26.

24. M.I. Levene HG, Caroline Sands , J.R. Moore Method of predicting outcomes in perinatal asphyxia. The Lancet. January 1986 327(8472):67-9.

25. Casey BM, McIntire DD, Leveno KJ. The continuing value of the apgar score for the assessment of newborn infants. N Engl J Med. 2001;344(7):467-71.

26. Horn Ar Fau - Swingler GH, Swingler Gh Fau - Myer L, Myer L Fau - Harrison MC, Harrison Mc Fau - Linley LL, Linley Ll Fau - Nelson C, Nelson C Fau - Tooke L, et al. Defining hypoxic ischemic encephalopathy in newborn infants: benchmarking in a South African population. LID - 10.1515/jpm-2012-0107 [doi] LID - /j/jpme.ahead-of-print/jpm-2012-0107/jpm-2012-0107.xml [pii]. (1619-3997 (Electronic)).

27. Grow J Fau - Barks JDE, Barks JD. Pathogenesis of hypoxic-ischemic cerebral injury in the term infant: current concepts. (0095-5108 (Print)).

28. Charlene MT Robertson MD FRCPC1 MPMBFLF. Follow-up of the term infant after hypoxic-ischemic encephalopathy. Paediatr Child Health. May/June 2006;11(5):278-82.

29. Jacobs S Fau - Hunt R, Hunt R Fau - Tarnow-Mordi W, Tarnow-Mordi W Fau - Inder T, Inder T Fau - Davis P, Davis P. Cooling for newborns with hypoxic ischaemic encephalopathy. (1469-493X (Electronic)).

30. Azzopardi Dv Fau - Strohm B, Strohm B Fau - Edwards AD, Edwards Ad Fau - Dyet L, Dyet L Fau - Halliday HL, Halliday Hl Fau - Juszczak E, Juszczak E Fau - Kapellou O, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. (1533-4406 (Electronic)).

31. Laptook AR. The neo.nEURO.network Hypothermia Randomized Controlled Trial. Pediatrics. 2010;126(4):e965-6. Epub 2010/09/22.

32. Wintermark P. Current controversies in newer therapies to treat birth asphyxia. International journal of pediatrics. 2011(1687-9759 (Electronic)).

33. Anne Hansen M, MPH, and Janet Soul, MD, CM. New induced hypothermia protocol Paediatric views [Internet]. February 2008

34. Sarnat Hb Fau - Sarnat MS, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. (0003-9942 (Print)).

35. Hannah Me Fau - Hannah WJ, Hannah Wj Fau - Hewson SA, Hewson Sa Fau - Hodnett ED, Hodnett Ed Fau - Saigal S, Saigal S Fau - Willan AR, Willan AR. Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. Term Breech Trial Collaborative Group. (0140-6736 (Print)).

36. Goffinet F Fau - Carayol M, Carayol M Fau - Foidart J-M, Foidart Jm Fau - Alexander S, Alexander S Fau - Uzan S, Uzan S Fau - Subtil D, Subtil D Fau - Breart G, et al. Is planned vaginal delivery for breech presentation at term still an option? Results of an observational prospective survey in France and Belgium. (1097-6868 (Electronic)).

Outcomes of neonates with perinatal asphyxia at a tertiary academic hospital in Johannesburg, South Africa

N Padayachee, MB ChB, DCH (SA); **D E Ballot**, MB BCh, FCPaed (SA), PhD

Department of Paediatrics and Child Health, University of the Witwatersrand and Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa

Corresponding author: *N Padayachee (natasha.padayachee@gmail.com)*

Background. Perinatal asphyxia is a significant cause of death and disability.
Objective. To determine the outcomes (survival to discharge and morbidity after discharge) of neonates with perinatal asphyxia at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).
Methods. This was a descriptive retrospective study. We reviewed information obtained from the computerised neonatal database on neonates born at CMJAH or admitted there within 24 hours of birth between 1 January 2006 and 31 December 2011, with a birth weight of >1 800 g and a 5-minute Apgar score <6.
Results. Four hundred and fifty infants were included in the study; 185 (41.1%) were females, the mean birth weight (± standard deviation) was 3 034.8±484.9 g, and the mean gestational age was 39.1±2.2 weeks. Most of the infants were born at CMJAH (391/450, 86.9%) and by normal vaginal delivery (270/450, 60.0%). The overall survival rate was 86.7% (390/450). Forty-two infants were admitted to the intensive care unit (ICU). The ICU survival rate was 88.1% (37/42). Significant predictors of survival were place of birth (p=0.006), mode of delivery (p=0.007) and bag-mask ventilation at birth (p=0.040). Duration of hospital stay (p=0.000) was significantly longer in survivors than in non-survivors (6.5±6.6 days v. 2.8±9.8 days). The remaining factors, namely gender, antenatal care, chest compressions, diagnosis of meconium aspiration syndrome or persistant pulmonary hypertension, did not differ significantly between the two groups. The rate of perinatal asphyxia (5-minute Apgar score <6) was 4.7/1 000 live births, and there was evidence of hypoxic ischaemic encephalopathy (HIE) in 3.6/1 000 live births. Of the 390 babies discharged from CMJAH, 113 (29.0%) had follow-up records to a mean corrected age of 5.9±5.0 months. The majority (90/113, 79.6%) had normal development.
Conclusions. (*i*) The high overall survival and survival after ICU admission provides a benchmark for further care; (*ii*) obtaining adequate data for long-term follow-up was not possible with the existing resources – surrogate early markers of outcome and/or more resources to ensure accurate follow-up are needed; and (*iii*) the high incidence of HIE suggests that a therapeutic hypothermia service, including a long-term follow-up component, would be beneficial.

S Afr J CH 2013;7(3):89-94. DOI:10.7196/SAJCH.574

Over 9 million children die each year during the perinatal and neonatal periods, and nearly all of these deaths occur in developing countries.[1] Perinatal asphyxia is a serious clinical problem globally. Every year approximately 4 million babies are born asphyxiated; this results in 1 million deaths and an equal number of serious neurological consequences ranging from cerebral palsy and mental retardation to epilepsy.[2] Perinatal asphyxia is a major factor contributing to perinatal and neonatal mortality, which is an indicator of the social, educational and economic standards of a community.

Perinatal asphyxia is defined as any perinatal insult resulting in suffocation with anoxia and increased carbon dioxide.[2] Severe fetal hypoxia or ischaemia can manifest in the newborn as encephalopathy, and may result in neonatal death or permanent motor and mental disability.[2]

Taking into account that neonatal deaths account for almost 40% of deaths of children under 5, it is apparent that Millennium Developmental Goal 4 (aiming at a two-thirds reduction in under-5 mortality by the year 2015 from a baseline in 1990) can only be met by substantially reducing neonatal deaths. Perinatal asphyxia is the fifth largest cause of under-5 deaths (8.5%) after pneumonia, diarrhoea, neonatal infections and complications of preterm birth.[2]

The death of an infant as a result of perinatal asphyxia is devastating and frequently avoidable. In developed countries with well-functioning health services these deaths are rare and ways to prevent them are widely understood and applied. However, a perinatal audit using the Perinatal Problem Identification Programme (PIPP) (www.ppip.co.za) has identified perinatal asphyxia as a common and important cause of death in South Africa.[3] At Chris Hani Baragwanath Hospital in Gauteng, 20% of all neonatal deaths are due to asphyxia.[4] A group of 25 term asphyxiated infants admitted to the Johannesburg Hospital Neonatal Unit was studied between September 1980 and March 1982. This study showed a mortality rate of 20%, 16% of children were disabled at the 2-year assessment, and 20% were lost to follow-up.[5] In a follow-up retrospective study of 109 term infants with moderate to severe perinatal asphyxia, prognosis was often poor, particularly in patients with seizures, cardiopulmonary signs of asphyxia and multi-organ dysfunction.[6]

The fundamental goal of establishing perinatal audits in areas with high perinatal mortality rates is to reduce the number of perinatal deaths through improvement in the quality of care. Several studies have shown a strong association between the establishment of an effective audit process and improvement of the quality of maternal health services and perinatal mortality rates.[3] Currently there are limited data on perinatal mortality rates, and although available figures are very high, they are likely to underestimate the problem.

The major difficulty in collecting accurate epidemiological data is lack of a common definition of the diagnostic criteria of perinatal asphyxia.[2] The umbilical artery pH that defines asphyxia of a sufficient degree to cause brain injury is unknown. Although the

most widely accepted definition is a pH of <7.0, even with this degree of acidosis the likelihood of brain injury is low.[7]

Means of assessment include umbilical pH, 1-hour post-delivery blood gas, Apgar scores, and neurological changes ranging from twitching to hypotonia and seizures. When resources are lacking in developing countries, perinatal asphyxia can be crudely assessed by use of the Apgar score.[8]

Apgar scores at 10 minutes provide useful prognostic data before other evaluations are available for infants. Low Apgar scores at 1, 5 and 10 minutes have been found to be markers of an increased risk of death or chronic motor disability.[9] More scientific methods have been used, but this is not possible in settings where resources are scarce.[10]

The major consequence of perinatal asphyxia is hypoxic ischaemic encephalopathy (HIE). Diagnosis of HIE requires abnormal findings on neurological examination the day after birth. The clinical spectrum of HIE is described as mild, moderate or severe according to the Sarnat stages of HIE. Infants can progress from mild to moderate and/or severe encephalopathy over the 72 hours following the hypoxic-ischaemic insult.[11] The terms 'perinatal asphyxia' and 'HIE' are often inappropriately used to define the same pathology. The problem of benchmarking definitions of HIE in the South African context has been specifically discussed in a recent publication. Horn *et al.* showed that there is wide variation in the incidence and grade of HIE, depending on which criteria are used.[12]

Until recently, solving the problem of perinatal asphyxia lay mainly in the obstetric realm. Prompt, effective neonatal resuscitation can improve outcome. This has been addressed by the development and implementation of the South African neonatal resuscitation programme,[13] endorsed by the South African Paediatric Association (SAPA).

Cerebral cooling has been shown to significantly improve the outcome for neonates with moderate HIE.[14] In order to effectively implement and monitor such intervention for perinatal asphyxia, it is necessary to have current data on neonates with perinatal asphyxia and those with HIE. Unlike with moderate to severe HIE, the association of perinatal asphyxia with brain damage is not defined, and perinatal asphyxia is not itself an indication for cerebral cooling. The aim of the present study was to review neonates with perinatal asphyxia and determine how many had HIE, the grade of HIE, factors associated with survival at discharge and morbidity on follow-up, and specifically the burden of disease of moderate to severe HIE, as this is the group that requires cooling.

Methods

This was a descriptive retrospective study. The study population included all neonates delivered at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from 1 January 2006 to 31 December 2011. Babies who were born before arrival (BBA) and those transferred from other hospitals were included if they arrived at CMJAH within 24 hours of birth. The total number of live births at CMJAH and the two major midwife obstetric units affiliated to the hospital was estimated to be 1 310 per month (2011 figures).

Babies were included in the sample if their birth weight was >1 800 g and their 5-minute Apgar score <6.[15] Sarnat and Sarnat classification was used for grading of HIE.[16] Depending on neurobehavioural signs, neonates were divided into stages 1, 2 or 3, which according to the classification correlate with the descriptions of mild, moderate and severe encephalopathy, respectively.[16] Not all babies were assigned a grade of HIE. The recorded discharge diagnoses were reviewed and cases with other evidence of possible encephalopathy (poor suck, lethargy, seizures, decreased tone or lack of responsiveness) recorded on the discharge diagnosis were also noted. These babies were presumed to have HIE, but they could not be graded retrospectively.

Babies with possible causes of low Apgar scores other than perinatal asphyxia, such as chromosomal abnormalities, obvious congenital abnormalities of the central nervous system, spinal muscular atrophy and conditions incompatible with life, were excluded from the study.[6] Those who had meconium aspiration or were subsequently proven to have neonatal sepsis were included.

All attending staff received training according to the SAPA guidelines so that they could start appropriate resuscitation immediately. Babies with grade 2 - 3 HIE were ventilated at the discretion of the attending physician and not routinely, because of resource constraints resulting in limited availability of neonatal intensive care unit (ICU) beds and ventilators. These babies received all other care including supplemental oxygen, fluids, anticonvulsants, nutrition and antibiotics as required. Cerebral cooling was only started at the end of the study period and was done in the ICU. Magnetic resonance imaging was not available during the study period.

Patient information was obtained from the computerised neonatal database at CMJAH, which is kept for clinical audit purposes. Standard information was collected prospectively by attending medical house staff and entered into a Microsoft Access programme by a data capturer. This included 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, mortality, duration of hospital stay, cerebral cooling, amplitude electroencephalogram (aEEG) findings, presence of meconium aspiration syndrome (MAS), persistent pulmonary hypertension of the newborn (PPHN), and presence of neonatal sepsis. Only culture-proven sepsis, both early (<72 hours) and late (>72 hours), was considered. The neonatal unit submits mortality data to the PIPP database (http://www.pipp.co.za). Final PIPP diagnosis was reviewed for all deaths.

On discharge of a patient, the parents/caretakers are given an appointment to visit our routine post-discharge neonatal follow-up clinic (NNFU), which is staffed by paediatricians, medical officers, occupational therapists, physiotherapists and speech therapists. Defaulters are contacted once in writing, no further attempt being made to ensure follow-up. Follow-up visits are recorded and stored in the clinic files. NNFU records were reviewed and the findings noted by the attending doctor and the multidisciplinary team were recorded. Outcomes at follow-up were recorded as normal neurological development (age-appropriate milestones achieved, normal vision and hearing), cerebral palsy and developmental delay, microcephaly, cortical blindness, hearing loss or seizures. The outcome at the last clinic attendance was noted for each patient.

Statistical analysis

Data were entered onto an MS-Excel spreadsheet and then imported to the statistical software SPSS version 20 for analysis using standard statistical methods. The analysis of patient demographics and baseline outcome variables was summarised using descriptive study methods and expressed as means (± standard deviations (SDs)) or medians (ranges) for continuous variables and frequencies and percentages for categorical variables. Survivors and non-survivors were compared. Categorical data were compared using chi-square analysis and continuous data using unpaired *t*-tests (as the distribution was normal).

Ethics approval

The study was approved by the Committee for Research on Human Subjects of the University of Witwatersrand (clearance certificate number M120447).

Results

A total of 470 babies were eligible for inclusion into the study; however, 7 were excluded because there were no clinical data available at all, and

Table 1. Clinical and demographic characteristics of neonates with perinatal asphyxia at Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg (*N*=450)

Characteristic	
Maternal age (years), mean±SD	25.6±6.1
Parity, median (IQR)	1 (1 - 9)
Antenatal care, *n* (%)	
Yes	306 (68)
No	73 (16.2)
Not recorded	71 (15.8)
Place of delivery, *n* (%)	
Inborn	391 (86.9)
Outborn	48 (10.7)
BBA	11 (2.4)
Mode of delivery, *n* (%)	
NVD	270 (60)
CS emergency	120 (26.7)
CS elective	19 (4.2)
Vaginal breech	9 (2)
Assisted vaginal delivery	1 (0.2)
Not recorded	31 (6.9)
Gestational age (weeks), mean±SD	39.1±2.2
Birth weight (g), mean±SD	3 034.8±484.9
Gender, *n* (%)	
Males	260 (57.8)
Females	185 (41.1)
Unknown	5 (1.1)
Apgar score, median (IQR)	
1 minute	3 (0 - 5)
5 minutes	4 (1 - 5)
10 minutes	6 (1 - 10)
Bag-mask ventilation, *n* (%)	
Yes	334 (74.2)
No	116 (25.8)
Chest compressions, *n* (%)	
No	406 (90.2)
Yes	44 (9.8)
Presence of seizures, *n* (%)	
No	363 (80.7)
Yes	87 (19.3)
MAS, *n* (%)	
No	357 (79.3)
Yes	93 (20.7)
PPHN, *n* (%)	
No	448 (99.3)
Yes	3 (0.7)
Culture-positive sepsis*, *n* (%)	
No	437 (97.1)
Yes	13 (2.9)
HIE,† *n* (%)	
Yes	347 (77.1)
No	103 (22.9)
HIE grade, *n* (%)	
1	58 (12.9)
2	66 (14.7)
3	34 (7.6)
ICU admission, *n* (%)	
No	408 (90.7)
Yes	42 (9.3)
Duration of hospital stay (days), median (IQR)	4 (0 - 76)

SD = standard deviation; IQR = interquartile range; BBA = born before arrival; NVD = normal vaginal delivery; CS = caesarean section; MAS = meconium aspiration syndrome; PPHN = persistent pulmonary hypertension of the newborn; HIE = hypoxic ischaemic encephalopathy; ICU = intensive care unit.

*Early and late.

†Discharge diagnosis (see text).

Table 2. Problems in pregnancy and birth of neonates with perinatal asphyxia at Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg (*N*=450)

Problem	*n* (%)
Fetal distress	91 (20.2)
Meconium-stained liquor	49 (10.9)
Fetal distress + meconium-stained liquor	39 (8.7)
Multiple problems	15 (3.3)
Cord around the neck	14 (3.1)
Prolonged second stage	9 (2.0)
Cord prolapse	4 (0.9)
Poor progress	4 (0.9)
Malpresentation	1 (0.2)
Cephalopelvic disproportion	1 (0.2)
Shoulder dystocia	1 (0.2)

13 owing to major congenital abnormalities. The final sample therefore consisted of a total of 450 babies, 185 females (41.1%) and 260 males (57.8%). The mean ±SD maternal age was 25.6±6.1 years and mean parity was 1 (interquartile range 1 - 9). Birth weights ranged from 1 800 to 4 596 g (mean ±SD 3 034.8±484.9 g), and the mean ±SD gestational age was 39.1±2.2 weeks. Clinical and demographic characteristics are set out in Table 1.

The majority of the babies were born at CMJAH (391/450, 86.9%) and by normal vaginal delivery (270/450, 60.0%). Problems in pregnancy were documented in 228/450 cases (50.7%) (Table 2), fetal distress being the most common (91/450, 20.2%).

Table 3. Univariate analysis for determinants of survival of neonates with perinatal asphyxia at Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg (*N*=450)

Characteristic	Survivors, *n*/*N* (%)	Non-survivors, *n*/*N* (%)	χ^2	*p*-value
Gender			0.212	0.899
Male	226/260 (86.9)	34/260 (13.1)		
Female	160/185 (86.5)	25/185 (13.5)		
Not recorded	4/5 (80)	1/5 (20)		
Antenatal care			2.731	0.255
Yes	265/306 (86.6)	41/306 (13.4)		
No	60/73 (82.2)	13/73 (17.8)		
Not recorded	65/71 (91.5)	6/71 (8.5)		
Place of delivery			10.129	0.006
Inborn	344/391 (88)	47/391 (12)		
Outborn	35/48 (72.9)	13/48 (27.1)		
BBA	11/11 (100)	0/11 (0)		
Mode of delivery			15.888	0.007
NVD	226/270 (83.7)	44/270 (16.3)		
CS emergency	106/120 (88.3)	14/120 (11.7)		
CS elective	19/19 (100)	0/19 (0)		
Vaginal breech	9/9 (100)	0/9 (0)		
Assisted delivery	0/1 (0)	1/1 (100)		
Not recorded	30/31 (96.8)	1/31 (3.2)		
Bag-mask ventilation			4.203	0.040
Yes	283/334 (84.7)	51/334 (15.5)		
No	107/116 (92.2)	9/116 (7.8)		
Chest compressions			3.724	0.540
No	356/406 (87.7)	50/406 (12.3)		
Yes	34/44 (77.3)	10/44 (22.7)		
MAS			1.724	0.189
No	314/357 (88)	43/357 (12)		
Yes	77/93 (82.8)	16/93 (17.2)		
PPHN			0.456	0.500
No	388/447 (86.8)	59/447 (13.2)		
Yes	3/3 (100)	0/3 (0)		
Culture-positive sepsis			0.345	0.557
No	379/437 (86.7)	58/437 (13.3)		
Yes	13/13 (92.3)	1/13 (7.7)		
HIE†			15	0
No	101/103 (98.1)	2/103 (1.9)		
Yes	289/347 (83.3)	58/347 (16.7)		
HIE grade			61.389	0
1	56/58 (96.6)	2/58 (3.4)		
2	53/66 (80.3)	13/65 (19.7)		
3	8/34 (23.5)	26/34 (76.5)		
Not recorded	273/292 (93.5)	19/292 (6.5)		
ICU admission			0.820	0.775
No	353/408 (86.5)	55/408 (13.5)		
Yes	37/42 (88.1)	5/42 (11.9)		

BBA = born before arrival; NVD = normal vaginal delivery; CS = caesarean section; MAS = meconium aspiration syndrome; PPHN = persistent pulmonary hypertension of the newborn; HIE = hypoxic ischaemic encephalopathy; ICU = intensive care unit.
*Early and late.
†Discharge diagnosis (see text).

A total of 346 babies (76.9%) had evidence of HIE, but only 158 (45.7%) of these had a grade of HIE recorded. The rate of perinatal asphyxia (5-minute Apgar score <6) was 4.68/1 000 live births, and there was evidence of HIE in 3.6/1 000 live births.

ICU admissions

Forty-two babies were admitted to the ICU, 15 females and 27 males. Of these 15 (35.7%) had MAS, 9 (21.4%) had hyaline membrane disease (HMD) and 3 (7.1%) had PPHN. The ICU survival rate was 88.1% (37/42). Two of the babies received cerebral cooling after perinatal asphyxia. They were monitored in the neonatal ICU and both survived.

Mortality

The overall survival rate was 86.7% (390/450). The causes of death according to the PIPP classification were as follows: perinatal asphyxia 53/60 (88.3%), meconium aspiration and perinatal asphyxia 3/60 (5.0%), HMD 1/60 (1.7%), group B streptococcal infection 2/60 (3.3%) and hypovolaemic shock 1/60 (1.7%). Significantly, more babies who died compared with those who survived had evidence of HIE (Table 3).

Comparison between survivors and non-survivors

Various factors were compared between the babies who survived and those who died (Tables 3 and 4). Place of birth (p=0.006), mode of delivery (p=0.007) and bag-mask ventilation at birth (p=0.040) were all significantly associated with survival. The duration of stay (p=0.000) was significantly longer in survivors. The remaining factors, namely gender, antenatal care, chest compressions, diagnosis of meconium aspiration syndrome and persistent pulmonary hypertension of the newborn, did not differ significantly between the two groups.

Follow-up

Of the 390 babies discharged from CMJAH, 113 (29.0%) had follow-up records to a mean ±SD corrected age of 5.9±5.0 months. The majority (90/113, 79.6%) had normal development. Details of the disabilities are shown in Table 5.

Table 4. Comparison of continuous variables between surviving and non-surviving neonates with perinatal asphyxia at Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg (N=450)

Characteristic	Survivors mean±SD	Non-survivors mean±SD	p-value
Maternal age (years)	25.6±6.1	26.2±6.8	0.579
Birth weight (g)	2 895.7±589.1	2 962.6±514.7	0.405
Gestational age (weeks)	38.1±2.9	38.6±2.3	0.175
Duration of hospital stay (days)	6.5±6.6	2.8±9.8	0

SD = standard deviation.

Table 5. Results on follow-up of neonates with perinatal asphyxia at Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg

Characteristic	n/N (%)
Records available	
No	277/390 (71)
Yes	113/390 (29)
Normal development	90/113 (79.6)
Cerebral palsy	13/113 (11.5)
Developmental delay	6/113 (5.3)
Microcephaly	1/113 (0.9)
Cerebral palsy and microcephaly	2/113 (1.8)
Developmental delay and microcephaly	1/113 (0.9)
Seizures	1.113 (0.9)

Discussion

This review shows that perinatal asphyxia remains a common problem at CMJAH, with approximately 6 admissions every month. In-hospital mortality was low (60/450, 13.3%), with the burden anticipated to be in the disabled survivors. Our rates of perinatal asphyxia and HIE were similar to those found by Horn *et al.*[12]

The 5-minute Apgar score is a poor indication of cerebral injury. In this study, 103 babies (22.9%) had no evidence of HIE, although 347 (77.1%) had signs of neurological compromise recorded. Attending staff do not routinely allocate a grade of HIE, and only 158 babies had a grade recorded. This is a very important omission, as it is a difficult thing to decide retrospectively. Possible reasons for the lack of proper grading or a detailed neurological examination may be related to challenges in a busy resource-constrained setting, lack of continuity of care (as different healthcare workers review patients daily), or healthcare workers not having been adequately trained on the criteria to examine for and the grading to allocate.

There are few population-based studies of HIE in sub-Saharan Africa, and the published criteria that are used to define and grade HIE are too variable for meaningful comparisons between studies and populations. Horn *et al.*[12] discuss the difficulties in consensus definitions and criteria of HIE. The data show that there is a wide variation in the incidence and grade of HIE, depending on which criteria are used. A more refined method of classifying perinatal asphyxia than the 5-minute Apgar score is required, possibly the TOBY[14] or CoolCap[17] definitions; however, these require special investigations. There is a need to encourage staff to assign an HIE grade accurately. The need for resuscitation at birth predicted outcome and could be included in the definition of perinatal asphyxia in resource-poor settings, where there is no means of arterial blood gas measurement or aEEG available.

Our busy resource-constrained setting, where only 74.2% of infants born with a 5-minute Apgar score <6 receive bag-mask resuscitation, presents major challenges. Before a cooling programme is implemented, it is essential to ensure adequate neonatal resuscitation and strict HIE grading of all asphyxiated neonates.

Our follow-up rate is unacceptably low at only 29.0% (113/390), and it was disappointing that the 2 babies who had received cerebral cooling were not brought for follow-up. Failure to attend for follow-up may be due to socio-economic factors and the low level of education of our patients' parents/guardians. It is possible that some asphyxiated babies died after discharge, or that disabled children are kept at home without access to healthcare. It is therefore not possible to report rates of post-discharge disability or mortality accurately. Of the 113 patients with follow-up data, 24 (21.2%) had disability.

The study results show that predictors of survival were mode of delivery, place of birth and resuscitation at birth. Elective caesarean section was associated with improved outcomes. Unexpectedly, all babies with vaginal breech deliveries survived. A study has shown that in fetal breech presentation, neonatal outcome was better with planned caesarean section than vaginal breech delivery.[18] In contrast, a study from Europe showed that neonatal outcome after planned vaginal breech delivery did not differ from outcome after elective caesarean section.[19] However, we do not know whether our breech deliveries were planned. All the babies BBA survived. It is possible that more severely asphyxiated babies died at home or were

dead on arrival at the hospital, but data relating to that information were beyond the scope of this study. Duration of hospital stay was shorter for babies who died than for those who survived, indicating that their condition was very severe and resulted in early death.

Study limitations

This was a retrospective study that relied on data from attending staff, with possible inaccuracies and loss of data. This study describes the incidence of perinatal asphyxia as defined by a 5-minute Apgar score <6, and there are insufficient data to comment on the incidence of moderate to severe HIE or on morbidity after discharge. Lack of a clear definition of HIE was a further limitation. A prospective follow-up study of babies who sustain perinatal asphyxia is warranted.

Conclusion

The study confirms that perinatal asphyxia remains a significant problem at CMJAH. The high overall survival and survival after ICU admission provide a benchmark for further care. There is a need to obtain adequate data for long-term follow-up, as this was not possible with the existing resources. Further research is required to establish consensus definitions that can be used for meaningful population studies and benchmarking of HIE. More resources to ensure accurate follow-up are needed, and the high incidence of HIE suggests that a therapeutic hypothermia service including a long-term follow-up component would be beneficial.

References

1. Hoque M, Haaq S, Islam R. Causes of neonatal admissions and deaths at a rural hospital in KwaZulu-Natal, South Africa. South African Journal of Epidemiology and Infection 2011;26(1):26-29.
2. Lawn JE, Manandhar A, Haws RA, Darmstadt GL. Reducing one million child deaths from birth asphyxia – a survey of health systems gaps and priorities. Health Res Policy Syst 2007;5(1):4. [http://dx.doi.org/10.1186/1478-4505-5-4]
3. Pattinson RC, ed. Saving Babies 2008-2009: Seventh Report on Perinatal Care in South Africa. http://www.pptp.co.za/downloads/Saving%20Babies%202008-9.pdf (accessed 21 June 2013).
4. Cooper PA, Patrick K. Analysis of term asphyxiated infants at Baragwanath Hospital. Proceedings of the Eleventh Conference on Priorities in Perinatal Care in South Africa. Johannesburg: Department of Paediatrics, University of the Witwatersrand, 1992.
5. Wild C, Rothberg AD, Cooper PA, Thompson PD, Cohn R. Outcome for premature infants versus full term asphyxia. Proceedings of the Third Conference on Priorities in Perinatal Care in South Africa. Johannesburg: Department of Paediatrics, University of the Witwatersrand, 1984.
6. Scher LG. Outcome following asphyxial insult in term neonates. MMed (Paed) thesis, University of the Witwatersrand, Johannesburg, 2000.
7. Thornberg E, Thiringer K, Odeback A, Milsom I. Birth asphyxia: Incidence, clinical course and outcome in a Swedish population. Acta Paediatr 1995;84(8):927-932. [http://dx.doi.org/10.1111/j.1651-2227.1995.tb13794.x]
8. World Health Organization. Birth Asphyxia – Summary of the previous meeting and protocol overview. 11 June 2007. http://www.curoservice.com/health_professionals/news/pdf/10-09-2007_birth_asphyxia02.pdf (accessed 5 August 2013).
9. Nelson KB, Ellenberg JH. Apgar scores as predictors of chronic neurologic disability. Pediatrics 1981;68(1):36-44.
10. Gregersen NE, Ballot DE, Guidozzi F, Cooper PA. Birth asphyxia, presenting a case for 'a stitch in time'. S Afr Med J 1999;89(3):326-332.
11. Robertson CM, Perlman M. Follow-up of the term infant after hypoxic-ischemic encephalopathy. Paediatr Child Health 2006;11(5):278-282.
12. Horn AR, Swingler GH, Myer L, et al. Defining hypoxic ischemic encephalopathy in newborn infants: Benchmarking in a South African population. J Perinat Med 2013;41(2):211-217. [http://dx.doi.org/10.1515/jpm-2012-0107]
13. Ballot D, Adhikari M, Bolton K, et al. South African Handbook of Rescusitation of the Newborn. Johannesburg: South African Paediatric Association, 2004.
14. Azzopardi DV, Strohm B, Edwards AD, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med 2009;361(14):1349-1358. [http://dx.doi.org/10.1056/NEJMoa0900854]
15. Misra PK, Srivastava N, Malik GK, et al. Outcome in relation to Apgar score in term neonates. Indian Pediatr 1994;31(10):1215-1218.
16. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: A clinical and electroencephalographic study. Arch Neurol 1976;33(10):696-705. [http://dx.doi.org/10.1001/archneur.1976.00500100030012]
17. Jacobs S, Hunt R, Tarnow-Mordi W, Inder TP, Davis P. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev 2007;(4):CD003311. [http://dx.doi.org/10.1002/14651858.CD003311.pub2]
18. Hannah ME, Hannah WJ, Hewson SA, Hodnett ED, Saigal S, Willan AR, Term Breech Trial Collaborative Group. Planned caesarean section versus planned vaginal birth for breech presentation at term: A randomised multicentre trial. Lancet 2000;356(9239):1375-1383. [http://dx.doi.org/10.1016/S0140-6736(00)02840-3]
19. Goffinet F, Carayol M, Foidart J-M, et al. Is planned vaginal delivery for breech presentation at term still an option? Results of an observational prospective survey in France and Belgium. Am J Obstet Gynecol 2006;194(4):1002-1011. [http://dx.doi.org/10.1016/j.ajog.2005.10.817]

Ethics Clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Natasha Padayachee

CLEARANCE CERTIFICATE	**M120447**
PROJECT	Outcomes of Neonates with Perinatal Asphyxia at CM Johannesburg Academic Hospital from 2007-2011
INVESTIGATORS	Dr Natasha Padayachee.
DEPARTMENT	Department of Paediatrics & Child Health
DATE CONSIDERED	04/05/2012
+DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 04/05/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof D Ballot

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...