

Are we doing better? Hypoxic Ischemic Encephalopathy in Pelonomi Hospital during two time periods

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DECLARATION

I, Dina Gertruida Bruwer, declare that this research report is my own work. It is being submitted for the Degree of Master of Medicine in Paediatrics at the University of the Free State, Bloemfontein, South Africa. It has not been submitted before for any degree or examination at this or any other academic institute.

Signed on _____ day of _____ 2016

DEDICATION

I would like to dedicate this research study to my husband and our two daughters Ava and Amélie. Thank you for believing in my dreams and for inspiring me to never stop fighting for what I believe in!



Today is YOUR day!
Your MOUNTAIN is waiting
So...get ON YOUR way.
-Dr. Seuss

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Abstract

Introduction: In 2007 a study was conducted in the Neonatal High care unit of Pelonomi Hospital in Bloemfontein which looked at the profile of neonates admitted with Hypoxic Ischemic Encephalopathy. In 2014, we replicated the study and compared the two study periods. This gave us the opportunity to assess the current burden of HIE and also to compare the two time periods to answer the question of whether there was an improvement in incidence and outcome.

Methods: A retrospective observational study was performed to compare data from 2007 and 2014. All neonates admitted with Hypoxic Ischemic Encephalopathy to the Neonatal High Care Unit of Pelonomi Hospital during the year 2014 were included in the study. Data from the 2007 study were obtained and used for comparison to the current cohort.

Results: Hundred and sixty one cases were included in the study, compared to 132 cases captured in 2007. The neonates diagnosed with HIE still comprised more than 10% of the total admissions in our unit. Two thirds of babies included in both studies were male. The majority of infants were born to primiparous mothers during both time periods. Teenagers proved to have a higher relative risk for HIE compared to the other age groups. Maternal factors identified that could play a possible role in the prediction of the grade of HIE, were pre-eclampsia and anaemia, as well as hypertension. The majority of infants were diagnosed as having grade 1 HIE with a slight increase in the number of grade 2 and a decrease in grade 3 cases in 2014. The relationship between the grade of HIE and the neurological outcome, as well as the general outcome, remained statistically significant. Hyperglycaemia in an infant with HIE stood out as a very strong predictor for a higher grade of HIE. In 2007 HIV infection was identified as one of the most common maternal risk factors but in our 2014 study there was a sharp decline in HIV positive mothers. Meconium exposure remained one of the top three risk factors for HIE. Booking late and or not at all for ante natal visits remain a major risk factor. Significant risk factors identified were a delay in referral, missing indicators of foetal distress and a prolonged second stage of labour without intervention. Inadequate theatre facilities, as a major preventable administrative risk factor, was accentuated once again. Although there were a decrease in HIE related deaths over the seven years, statistical significance was not reached. The number of babies classified as having abnormal neurology on follow up, increased in 2014.

Conclusion: HIE, although mostly preventable, remains a major burden in South African hospitals, including Pelonomi Hospital. "Are we doing better?" If we look at our results, and the comparison between the two time periods, the answer may be a rather unfortunate "not yet".

1. Introduction and Literature review

In 2007 a study was conducted by Dr AE van der Vyver, a consultant in the Department of Paediatrics in the Neonatal High Care Unit of Pelonomi Hospital to describe the profile of neonates admitted with Hypoxic Ischemic Encephalopathy.¹ This was done because HIE remains a serious health burden with major health care implications despite preventative measures being put in place.

Previous Global Burden of Disease (GBD) estimates identified “Birth asphyxia” as one of the conditions which caused the highest numbers of disability adjusted life years (DALYs) for any single condition²

In 2010 GBD intrapartum-related conditions comprised 50.2 million DALYs (2.4% of total) and 6.1 million years of life with disability. The same study found that 96% of babies born with intrapartum-related encephalopathy, were born in low- and middle income countries.³ The World Health Organization (WHO) World Health Report 2005 estimated that as many as 1 million survivors of intrapartum related complications, may develop cerebral palsy, learning difficulties or other disabilities.⁴ The impact of intrapartum asphyxia on an already struggling health system thus cannot be ignored.

Childbirth related complications is estimated to cause 814 000 neonatal deaths annually,⁵ and globally, intrapartum related deaths is the 3rd most common cause of neonatal deaths after preterm death and infections.⁶ Only measuring mortality however sets the bar too low and the impact of many children not reaching their optimal potential also needs to be taken into account.

‘The Levels and Trends in Child Mortality’ report, developed annually by the United Nations Inter-Agency Group for Child Mortality Estimation, is led by the United Nations Children’s Fund (UNICEF) and includes the WHO, the World Bank Group and the United Nations Population Division of the Department of Economic and Social Affairs. This 2014 report concluded that 2,8million (45%) of all under five deaths for 2013 occurred during the neonatal period, with the major causes of neonatal mortality being complications due to pre-term birth (35%) or problems during delivery or birth (24%).

The neonatal period, that is the first 28 days of life, represents a vulnerable time in a newborn’s life.⁷ Newborn survival has gained rapid attention in recent years, but attention has yet to translate into appropriate action.⁸ The proportion of neonatal deaths in the under-five age group, has increased in all WHO regions over the last 20 years.⁹

The latest report from the WHO (2015) reveals that the total number of neonatal deaths decreased from 4.7 million in 1990 to 2.8 million in 2013 and that neonatal mortality rates per 1000 live births declined from 33 to 20 over the same period, which is a reduction of 39%. However, the proportion of deaths in children aged less than 5 years that occurred in the neonatal period, has increased from 37% in 1990 to 44% in 2013.¹⁰

These early neonatal deaths in the first week of life has been identified as the statistic making the least progress toward the Millennium developmental Goal (MDG) 4 of the WHO.¹¹

Less than one third of all countries have either achieved or were on track to meet the MDG target by 2015.⁵

The results released by the WHO reveals that South Africa managed a reduction of only 28%, which is far below the target (67%) acquired to reach the MDG for reduction in under 5 year mortality by 2015.⁵

A study conducted in South Africa from October 1999 till September 2003 found that 32.4% of neonatal deaths were related to asphyxia-hypoxia and in 72% of these deaths, the most common diagnosis was intrapartum asphyxia. The main cause of death was identified as Hypoxic Ischemic Encephalopathy (HIE).¹² The prevalence of intrapartum related birth asphyxia in developing countries remains high (4.8/1000 births) in comparison to developed countries where it is decreasing and has a much lower incidence (1.5/1000 births)^{13,14}

The eighth 'Saving Babies Report' of 2010 - 2011, which looked at avoidable risk factors contributing to perinatal outcome in South Africa, has once again identified intrapartum asphyxia as one of the major causes of perinatal death.¹⁵ Pelonomi Hospital Neonatal Care Unit forms part of the 94% of South African Hospitals included in the latest report of the Perinatal Problem Identification Programme (PIPP).

According to this report the Free State has the highest Perinatal Mortality Rate (43.12/1000 births) in South Africa. The Northern Cape is second at 33.66/1000 births. The Free State also have the highest Stillbirth Rate (30.73/1000 births), Fresh Stillbirth Rate (4.75/1000 births) and Early Neonatal Death Rate (5.70) for babies above 2,5kg - the latter two reflecting the quality of intrapartum care.¹⁶ Therefore a closer look into the avoidable risk factors of intrapartum asphyxia in Free State Hospitals was imperative. The fact that data exists on the epidemiology of HIE in our institution for a previous time period gave us the opportunity to assess the current state of HIE and also to compare the two time periods.

HIE can be caused by ante-, intra- and postpartum events¹⁷

Antepartum risk factors	Intra partum risk factors	Infant / post-natal risk factors
Primiparity ^{18,19}	Malpresentation ²¹	Prematurity ²⁰
Febrile illness ²¹	Prolonged labour ^{22,23}	Low birth weight ²¹
Pregnancy induced hypertension ^{18,19,23}	Maternal Pyrexia ²¹	Intrauterine growth restriction ²³
Severe pre-eclampsia ²¹	Meconium stained liquor ^{18,21}	
Anaemia ¹⁸	Premature rupture of membranes ²¹	
Antepartum hemorrhage ^{18,21}	Oxytocin augmentation ²¹	
	Umbilical cord prolapse ²³	

Table 1: Antepartum, intrapartum and infant risk factors for "birth asphyxia" as reported by previous hospital based studies

Recent studies support a combination of the above mentioned factors.²⁴ Unavoidable risk factors must be anticipated and screened for early enough. The focus remains on preventable factors.

After conducting a thorough literature study, a data form was compiled to assist with identification of these factors. This information was interpreted with the focus of the PPIP programme in mind. The PIPP, as mentioned above, is an important tool that is used for the assessing of perinatal quality of care through auditing of perinatal deaths. These guidelines categorize avoidable risk factors in patient-, medical, personnel- and administrative associated factors.²⁵

Clinical audit is an essential step to improve care and it is important to confirm changes in morbidity and mortality patterns in babies with HIE. The findings and possible interventions brought about by findings of the PPIP programme has long term implications for ameliorating the burden of death and disability on society.²⁶ We felt our study could contribute to this project of ultimately improving the future of newborns in South Africa.

2. Concepts and definitions

2.1 Hypoxia and Ischemia

Hypoxia is the decreased oxygenation of cells or organs.

Ischemia refers to blood flow to cells or organs that is insufficient to maintain their normal function.²⁷

2.2 Asphyxia

A condition that occurs when there is an impairment of blood gas exchange which causes hypoxemia and hypercapnia.²⁸ The word ‘asphyxia’ is derived from the Greek word ‘asphuxia’, which literally means “stopping of pulse”. Hypoxia and metabolic acidosis result from hypoventilation.²⁹

2.3 Birth asphyxia and intrapartum asphyxia

Birth asphyxia is defined by the World Health Organisation as “the failure to initiate and sustain breathing at birth.”³⁰

American Academy of Paediatrics/American College of Obstetrics and Gynaecology (1996) ³¹	American College of Obstetrics and Gynaecology (2002) ³² (ACOG)	International Cerebral Palsy Task Force (1999) ³³ (ICPTF)
Essential:		
<ul style="list-style-type: none"> Profound metabolic acidosis (pH<7.0) 	<ul style="list-style-type: none"> Metabolic acidosis (pH<7.0 and base deficit ≥12mmol/L) 	<ul style="list-style-type: none"> Metabolic acidosis in early neonatal blood sample (pH<7.0 and base deficit ≥12mmol/L)
<ul style="list-style-type: none"> Apgar score ≤3 after 5 minutes 	<ul style="list-style-type: none"> Apgar score ≤3 after 5 minutes 	<ul style="list-style-type: none"> Apgar score ≤6 after 5 minutes
<ul style="list-style-type: none"> Neonatal encephalopathy 	<ul style="list-style-type: none"> Moderate or severe encephalopathy 	<ul style="list-style-type: none"> Moderate or severe encephalopathy
<ul style="list-style-type: none"> Multi organ system dysfunction 	<ul style="list-style-type: none"> Cerebral palsy of spastic quadriplegia or dyskinetic type 	<ul style="list-style-type: none"> Cerebral palsy of spastic quadriplegia or dyskinetic type
	<ul style="list-style-type: none"> Exclusion of other pathologies of cerebral palsy 	

Table 2: Consensus statements on diagnosing intrapartum asphyxia

The **diagnosis of intrapartum asphyxia** has been addressed by three consensus statements since 1996, giving more clarity to a still challenging dilemma, namely the fact that there is no single gold standard for an accurate diagnosis. (Table 1)

The American College of Obstetrics and Gynaecology and the International Cerebral Palsy Task Force also includes criteria suggestive of intrapartum timing.

Both state a sentinel event, abrupt change in foetal heart, multi system involvement and imaging evidence to be suggestive with the only difference being an APGAR score of ≤ 3 beyond 5 minutes according to ACOG and a score of < 6 beyond 5 min for CPTF criteria.

When a neonate cannot compensate due to severe asphyxia, hypoxic ischemic encephalopathy develops.³⁴

The task group recommend against using the term “birth asphyxia” unless there is clear evidence of an intrapartum related cause.³⁵ Therefor a shift away from the term “birth asphyxia” is the current trend and the term “intrapartum- related” should rather be used when referring to death due to asphyxia.³⁶

2.4 Neonatal Encephalopathy

Clinically, Neonatal Encephalopathy is a well-defined syndrome of abnormal neurological function in the earliest days of life in the term infant. It is manifested by difficulty in initiating and maintaining respiration, depression of tone and reflexes, abnormal level of consciousness and often by seizures.³⁷

2.5 Hypoxic Ischemic Encephalopathy

HIE is a permanent brain injury due to a lack of oxygen or adequate blood flow to the brain.³⁸ This leads to a syndrome of abnormal neurological behaviour in the neonate and is frequently associated with a multisystem dysfunction.³⁹ It can only be termed HIE if there is evidence that intrapartum hypoxia is the cause of the encephalopathy.⁴⁰

2.6 Grading of Hypoxic Ischemic Encephalopathy

A clinical grading by Sarnat and Sarnat⁴¹ (Based on the Modified Sarnat- Sarnat Score⁴²) was used as criteria for diagnosis of HIE. The grading is based on the response of infants to handling, their level of consciousness and changes in reflexes or tone. The presence of seizures also form part of the grading. This grading can predict the neurodevelopmental outcome on basis of the degree of HIE.⁴³

Clinical finding	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Conscious level	Irritable/hyper alert	Lethargic	Comatose, stuporous
Tone	Mildly abnormal (Hypo- or hypertonic)	Moderately abnormal (Hypotonic or dissociated)	Severely abnormal: Flaccid (Hypotonic)
Seizures	Absent	Present	Present
Primitive reflexes	Exaggerated	Depressed	Absent

Table 3: Modified Sarnat-Sarnat Score for criteria for diagnosis of HIE

3. Methodology

3.1 Study design

A retrospective observational study was performed to compare data from 2007 and 2014.

3.2 Study population

All neonates admitted with Hypoxic Ischemic Encephalopathy to the Neonatal High Care Unit of Pelonomi Hospital during the year 2014 were included in the study. Data from the 2007 study¹ were obtained and used for comparison to the current cohort.

3.3. Inclusion criteria

To strengthen the comparative aspect of the study, the same criteria as used by Dr. van der Vyver's study was required.

The following criteria was set:

- a gestational age of 36 weeks or more
- admission to the High Care unit with a clinical diagnosis of HIE
- an available patient file for completion of the data form

3.4 Exclusion criteria

The following neonates were excluded from the study:

- a gestational age of less than 36 weeks
- congenital and/or chromosomal abnormalities
- Incomplete files

3.5 Measurement

3.5.1 Data form

The same first three pages of the data form (see Appendix) was used as compiled in 2007 for the comparative study to ensure homogeneity. The only adjustment made was the address option in the "maternal history" section, as the boundaries of the districts have changed since 2007.

To gain some more information an "Additional Information from file" page with extra patient and maternal information was added as page 4 of the data form. More detail with regards to the outpatient follow up was also added as it was noticed that follow up was poor due to wrongly classified grade of HIE or defaulting. The neurological status at follow up was also noted, as it can give important information which may be used in future studies regarding HIE outcome.

3.5.2 Process

The Pelonomi Hospital's Meditech System was used to obtain the names of newborns possibly qualifying for the study. The admission register in the Neonatal High Care Unit and monthly statistics kept by the doctors in the unit ensured that all relevant patients were reviewed.

Both patient and maternal files were obtained from the hospital archive. Information was captured on the predesigned data forms by Dr. Dina Bruwer. All information of participants who complied with the inclusion criteria and for whom no exclusion criteria existed, were recorded on the data forms. Record was kept of all files excluded from the study. Missing or incomplete files were also noted as per exclusion criteria.

The degree of HIE was based on the Modified Sarnat and Sarnat definition (see Table 3) and was used as the diagnostic criteria for HIE. Data were recorded based on Maternal History, birth details, evidence of asphyxia and medical risk factors (ante-, intrapartum and specific newborn factors). The PIPP criteria were used to identify contributing risk factors with regards to HIE and were divided into patient-, medical personnel- and administrative factors. The outcome was also noted. An additional page with extra patient and maternal information was also completed. Any information that could play a role in better identifying risk factors for HIE was recorded. Patient follow up at the Neonatal High Risk Clinic and subsequent neurological outcome was also recorded when available. Information of patients who missed follow up due to wrong classification of HIE, defaulting or no appointment booked, was recorded.

All files were returned to the archive as soon as data was captured.

3.6 Statistical Analysis

The Department of Biostatistics of the University of the Free State performed the analysis of the data, using SAS/STAT software, version 9.4 for Windows. Associations between categorical variables were tested using chi-square analyses, with Fisher's exact p-values where small cell sizes were encountered. The mean days spent in the Neonatal High-Care Unit (NHCU) for those infants who had and had not experienced foetal distress was compared by means of a Student's t-test. Logistic regression was performed to determine whether the level of HIE (not the presence or absence of HIE) could be predicted by various categorical predictors. The risk and relative risk of HIE by age category was determined by comparing the current study data to values obtained from the PIPP data. Furthermore, data from the current study was compared to the 2007 data using chi-square analyses and the calculation of relative risks for the two cohorts.

3.7 Ethical considerations

The study was approved by the Ethics Committee of the Faculty of Health Sciences of the University of the Free State (Ethics Number ECUFS 26/2015). Written consent to conduct the study was also obtained from the Clinical Head of Pelonomi Hospital, Dr Benganga.

4. Results

Between 1 January and 31 December 2014, there were a total of 1527 admissions in the Neonatal High Care Units of Pelonomi Hospital. Out of these 1527 admission, 197 files were found to possibly fit the study profile. Twenty five of these files were excluded due to incomplete files, prematurity, inaccurate diagnosis and congenital abnormalities. Seven of these babies were transferred to Universitas, 1 with choanal atresia, 2 for cooling and 4 with meconium aspiration and or pulmonary hypertension for ventilation. The two cooling patients had insufficient information available to complete data forms as their files were sent with them to Universitas and could therefore not be included. Of the remaining 172 files identified, 11 files (6%) had to be excluded due to missing files. A total number of 161 files were then available for data collection, representing 92% of the 172 potential files identified. (See Figure 1).

The confirmed cases of HIE (n=161) represented 10.5% of the total number of admissions to the unit in 2014.

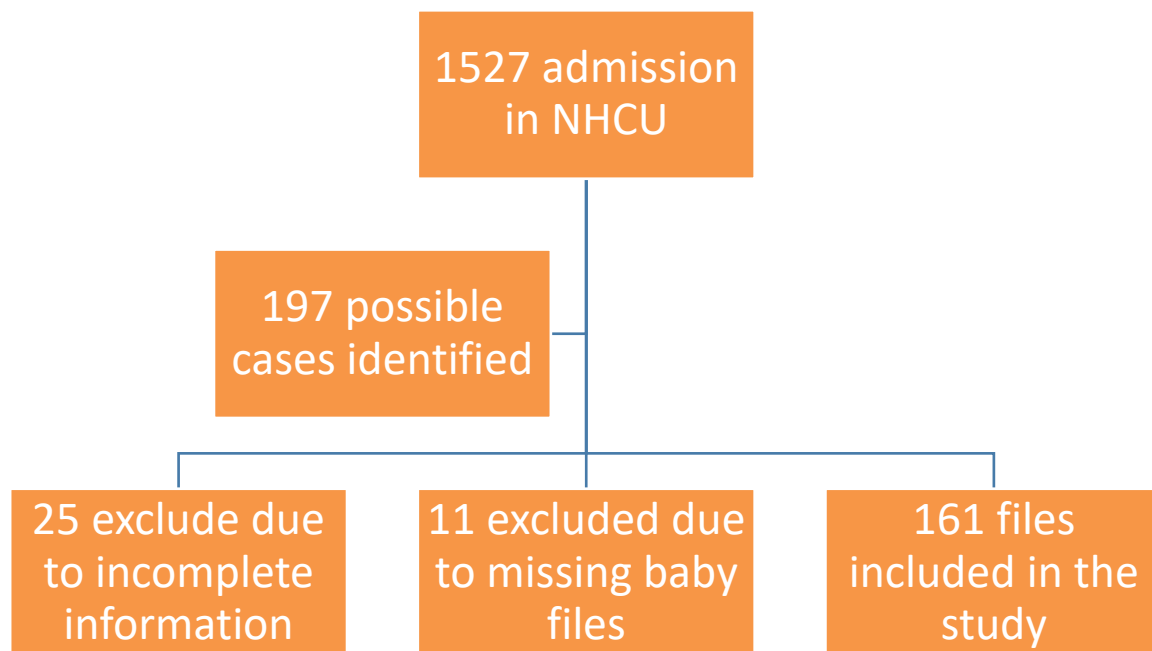


Figure 1. Flow chart of file processing

4.1 Maternal and birth history

Only 4 cases (2.48%) came from outside Pelonomi's referral area with the majority of babies (n=157; 97.5%) being referred from either Mangaung Metro or Xhariep districts. More than three quarters (n=122; 75.78%) of infants were born in Pelonomi Hospital and 59.80% of these mothers were referred to the hospital during labour. Thirty nine (24.2%) babies were born outside of Pelonomi, of which two were born at home or in transit. The place of delivery (in- or outside Pelonomi) proved to be significant with regards to outcome ($\chi^2=9.36$, df [degrees of freedom]=1, P_f [Fisher's Exact Test]=0.0068), with 97.5% of those born in Pelonomi surviving to discharge, compared to only 84.6% of those born outside. Outcome was also influenced by the place of birth outside of Pelonomi ($\chi^2=11.6166$, df=2, $P_f=0.0278$) All the patients in this study who were born at home or in transit, passed away. The place of delivery was also significant when looking at the neurological status prior to discharge ($\chi^2=7.2357$, df=1, $P_f=0.0124$). Twenty four percent of babies born outside of Pelonomi had an abnormal outcome whereas only 7% of the babies born in Pelonomi were deemed to have abnormal neurology at discharge. Seventeen babies were born at local clinics and 20 babies were born at other hospitals. It is important to note that the grade of HIE with regards to the place of delivery was statistically significant ($\chi^2=8.26$, df=2 and $p=0.0161$) A slightly larger percentage (54%) of grade 3 HIE babies were born outside of Pelonomi.

The age of the mothers were categorized as younger than 20 years, 20-35 years, and older than 35 years. Teenage mothers represented 22.98% (n=37) of the different age groups, i.e., 37 of the study babies were born to mothers younger than 20 years of age. Nine (5.59%) mothers were older than 35 years with the remaining hundred and fifteen (71.43%) infants' mothers being between 20 and 35 years of age. (See Figure 2A)

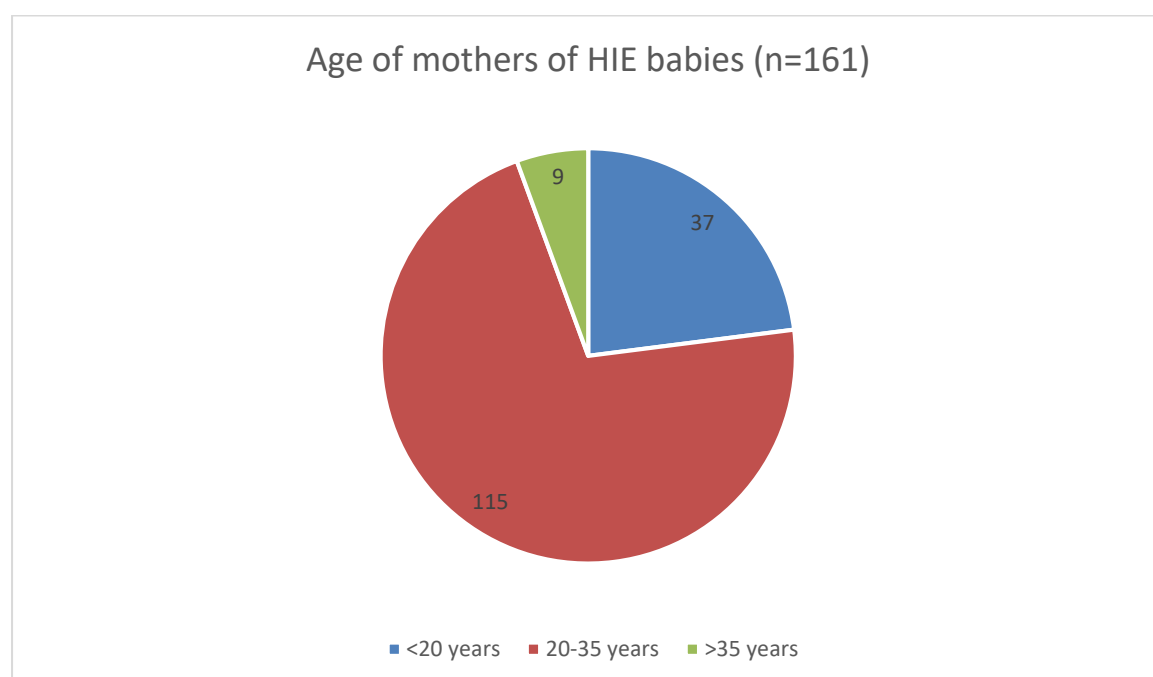


Figure 2a. Age of mothers of babies included in the study

It was found that age statistically increased the risk for HIE. PIPP data of 2014 (see Figure 2B) provided the number of different age groups of pregnant women in Pelonomi Hospital. It has to be taken into account that the PIPP data uses 34 as the upper age limit and in our study an upper age limit of 35 is used. Therefore only an approximate relative risk could be calculated. Teenagers proved to have a higher relative risk of HIE compared to the other age groups. In our population 30-33 year old woman also had a 2.61 higher risk compared to women >35 years of age. (See Table 4)

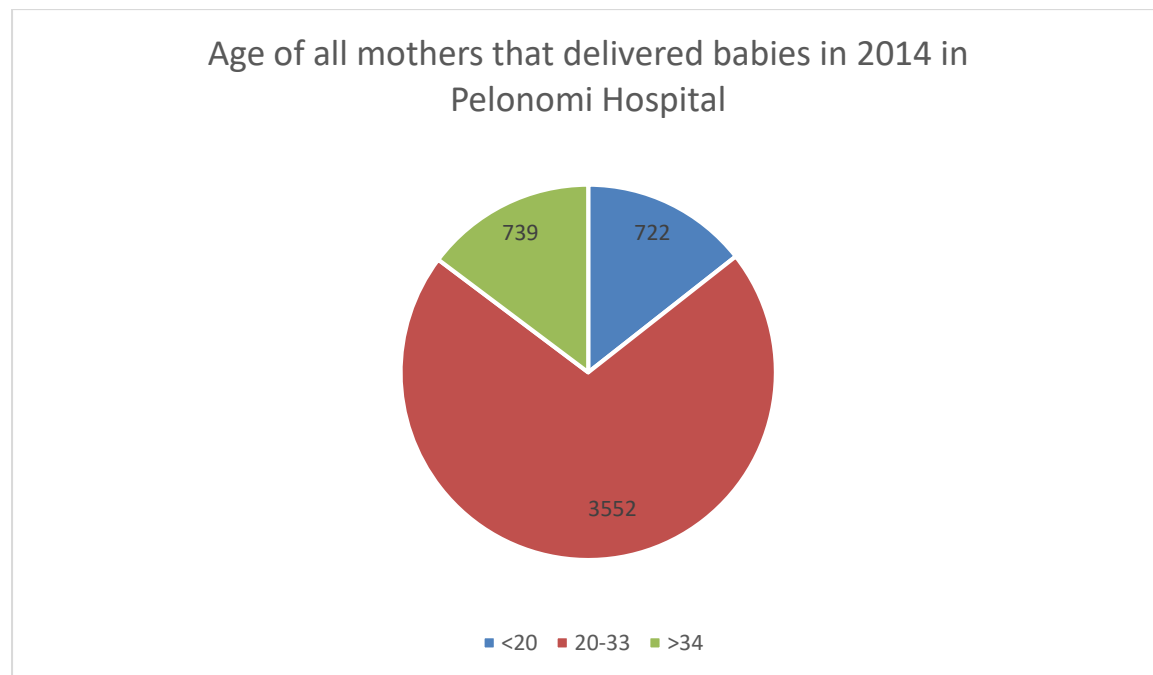


Figure 2b. PIPP data of all pregnant women in Pelonomi Hospital in the year 2014²⁵

Age group	Risk	Relative risk with 95% CI	
		20-33	>34
<=19	0.049	1.08 1.55 2.23	1.97 4.05 8.34
20-33	0.031		1.33 2.61 5.11
>34	0.012		

Table 4. Relative risk of age in relation to HIE risk calculation

With regards to the babies' gender, just under two thirds were noted to be male infants (n=99; 61.49%).

In this study, only three (1.86%) pregnancies were post mature (>42weeks gestational age). The majority of pregnancies lasted 36-42 weeks.

The vast majority of infants were born to primigravida mothers (n=96; 59.63%). Seven infants were identified to be mothers of grand multiparity, with one mother being pregnant for the seventh time.

With regards to HIV status one hundred and twenty-four mothers tested HIV negative (77.54%) with 34 (21.25%) mothers being positive and only 2 mothers the HIV status was unfortunately unknown.

Caesarean sections were done in the most cases (n=92; 57.50%) with 57 (35.63%) normal and 11 (6.88%) assisted vaginal deliveries. In only one case the type of delivery was unsure due to poor notes.

Ten (6.21%) large for gestational age babies were included in the study with 23 (14.29%) being small for gestational age and the rest (n=128; 79.50%) normal weight for gestational age.

Foetal distress was diagnosed in 53.16% (n=84) of infants. In three infants no confirmation regarding foetal distress could be found. Almost half of these infants (n=34; 48.57%) had a delay of more than two hours from diagnosis of foetal distress until delivery took place. Six (8.57%) were delivered within 1 hour from diagnosis and thirty (42.86%) had a delay between 1-2 hours prior to delivery. In the remaining infants (n=14; 20%) no data regarding the delay in time to delivery was available.

4.2 Asphyxia and outcome

Most infants were resuscitated by a Paediatric Registrar (67 cases; 41.61%), with resuscitation by midwives being second at 25.47% (n=41) and with an almost equal number of resuscitation done by interns (n=26; 16.15%) and medical officers (n=23; 14.29%). Neurological outcome on follow up was normal in 96% of cases when resuscitated by an intern, 95% normal when resuscitated by a registrar and with no deaths reported when resuscitated by a midwife. (See Table 6 and Figure 5 in discussion). The outcome with regards to the resuscitator was statistically significant ($\chi^2=14.3369$, df=4, $P=0.0165$). In more than half of the deaths (55%) the babies were reported to be resuscitated by a medical officer.

More than half of the infants (n=84; 52.17%) were classified as having grade 1 HIE with sixty four (39.75%) classified as grade 2 and 13 cases (8.07%) as grade 3. Twenty six (17.11%) babies were wrongly classified as grade 1 with a clear clinical picture of grade 2 features (the adjusted grading was taken into account). The relationship between the grade of HIE and the neurological outcome ($\chi^2=11.0381$, df=2, $P=0.0024$) as well as the general outcome ($\chi^2=108.5283$, df=2, $p<0.001$) was statistically significant. Ninety six percent of grade 1 HIE babies had normal neurology prior to discharge with 20% of grade 2 and a quarter of grade 3 babies being classified as "neurologically abnormal" at discharge.

All the grade 1 HIE patients survived to discharge, compared to a 69.23% mortality of the patients diagnosed as grade 3 HIE.

Thirty one (19.25%) neonates presented with convulsions and 27 (16.77%) required one or two anticonvulsants to eliminate symptoms. In an additional 4 (2.48%) neonates more than two anticonvulsants were needed to suppress convulsions. The number of anticonvulsants required by a neonate was statistically significant with regards to outcome ($\chi^2=5.1640$, $df=2$, $P_f=0.0490$) and neurological status at discharge ($\chi^2=16.2149$, $df=1$, $p<0.001$). Therefore, babies presenting with convulsions had a worse neurological outcome and the more resistant the convulsions were to treatment, i.e. requiring more than one anticonvulsant, the worse the outcome.

On discharge infants were classified as neurologically normal or abnormal, based on clinical notes (neurological status/outcome). Seventeen (11.18%) were classified as abnormal. Clinic follow up was also taken into account. Five neonates were classified as “normal” on discharge, but had abnormal neurological sequela on follow up at the clinic. Two of the 17 “abnormal” on discharge neonates had a normal follow up and 3 were still noted as having abnormal neurology. Six unfortunately defaulted follow up and in six of the “abnormal” neurology infants no follow up was booked.

All nine deaths (5.59%) were classified as having grade 3 HIE. In 2014 the total number of deaths in the unit was 118 neonates. HIE therefore accounts for almost 10% of all deaths (7.6%, 95% CI: 4.1%–13.9%).

4.3 Medical risk factors

Primiparity was identified as one of the most common medical risk factors, but was not proven to be a risk factor for worse outcome in HIE ($\chi^2=0.9129$, $df=1$, $P_f=0.4867$).

A third of mothers had anaemia, defined as a haemoglobin level of $<12\text{g/dL}$ ($n=51$; 31.68). Most mothers did not have fever and pregnancy induced hypertension and pre-eclampsia was not identified in the majority of cases. Antepartum haemorrhage, a history of a previous neonatal death and premature rupture was only relevant in a few cases. In 28 (17.39%) cases oxytocin was used to induce labour. Four cases (2.48%) presented with umbilical cord prolapse.

Fifty nine (36.65%) mothers presented with prolonged labour and in more than half of cases ($n=87$; 54.04%) meconium was noted.

Low birth weight and intrauterine growth restriction was identified in only 30 (18.63%) cases.

4.4 Contributing avoidable risk factors

Patients who booked late in pregnancy was identified as the number one modifiable contributing risk factor (n=24 (14.91%). In 5.59% (n=9) cases the mother never initiated ante natal care or had infrequent visits. In 27 cases (16.77%) a delay in referral to a secondary hospital was noted.

Foetal distress was not detected, although the baby was monitored, in 6.21% of mothers (n=10) and in another ten cases poor management of second stage of labour was noted specifically prolonged labour with no intervention. Inadequate theatre facilities was identified as the most important administrative risk factor (n=41; 25.47%). Lack of transport, institution to institution, also proved to be a problem with 35 cases noted (21.75). In 4 cases an insufficient number of doctors available (2.48%) was noted as a modifiable risk factor.

4.5 Additional Information

Forty four (27.33%) neonates presented with hypoglycaemia (glucose less than 2.6mmol/l) during the first 24h of admission. Hyperglycaemia (glucose level of >8.3mmol/l) was noted in 16 (9.94%) of patients. Hyperglycaemia was found to be statistically significant with regards to outcome ($\chi^2=12.68$, df=1 and $P=0.0062$). Babies without hyperglycaemia had a 96.6% survival rate compared to a 75% survival rate of those with hyperglycaemia. Meconium aspiration syndrome was diagnosed in 31(19.88%) neonates and cephalo-pelvic disproportion was noted in 31 cases (19.25%).

The auditing of maternal files was unfortunately a major problem as 37 (22.98%) files were not available (i.e., babies born at a clinic or another hospital) and the files were not found in 14 cases (8.70%).

Logistical regression was applied to the 2014 study to look at the relationship of maternal risk factors and preventable factors as per PIPP data with regards to grade of HIE (not the occurrence of HIE). Two separate logistic regression analyses were carried out, one for maternal factors and the other for child-related factors.

The maternal factors identified that could play a possible role in the prediction of the grade of HIE were pre-eclampsia (Odds ratio: 0.208 95% CI: 0.049–0.883) and anaemia (Odds ratio: 0.158 95% CI 0.064–0.389), as well as hypertension (Odds ratio: 2.659 95% CI: 1.014–6.972). Interestingly, in this specific population, mothers with pre-eclampsia and anaemia appeared to have a statistically significant chance of having babies with a *lower* grade of HIE, while mothers with pregnancy induced hypertension had a statistically significant chance of having babies with a higher grade of HIE.

Two variables which fell just short of significance in the logistic regression model were prolonged labour (p=0.069 Odds ratio 0.494 95% CI 0.231–1.057) and being a teenage mother (p=0.058 Odds ratio 2.292 95% CI 0.972–5.403), with the former seeming to predict a lower grade of HIE, and the latter a higher grade. The only child-related factor which was statistically significant was hyperglycaemia, which stood out as a very strong predictor for a higher grade of HIE (p<0.0001 Odds ratio 9.541 95% CI 3.022–30.125).

4.6 Comparison with the 2007 study

	Table 5. Comparison of HIE grades with regards to specific parameters in 2007 and 2014											
	Sarnat-Sarnat grading of HIE											
	Grade I				Grade II				Grade III			
	2007 (n=72)		2014 (n=84)		2007 (n=44)		2014 (n=64)		2007 (n=16)		2014 (n=13)	
	n	%	n	%	n	%	n	%	n	%	n	%
Infants dx with HIE *	72	54.5	84	52.17	44	33.3	64	39.8	16	12.1	13	8.07
Foetal distress #	18	25	43	51.19	16	36.4	35	41	5	31.3	6	7.14
Location of birth												
Born in Pelonom Hospital (n2007=101, n2014=122)	64	63.4	69	56.6	27	26.7	47	38.5	10	9.9	6	4.9
Born outside Pelonom Hos pital (n2007=31, n2014=39)	8	25.8	15	38.5	17	54.8	17	43.6	6	19.4	7	17.9
Clinical Outcome**												
Neuro- logically normal	72	100	81	96.43	32	72.7	51	79.7	2	12.5	3	75
Neuro- logically impaired	0	0	3	3.57	9	20.5	13	20.3	2	12.5	1	25
Death	0	0	0	0	3	6.8	0	0	12	75	9	69.23

* n2007=131,n2014=161

Number and percentage of infants who showed fetal distress per HIE grading group

** Number and percentage of infants' clinical outcome per HIE grading group

The percentage of confirmed HIE cases remained above 10% of total admissions to the unit. Between 2007 and 2014 the Southern Free State districts were changed from District 16 and 17 to consist of Mangaung Metro and Xhariep. The number of patients residing outside of the referral area reduced from 10 in 2007 to 4 in 2014.

Approximately a quarter of patients who were admitted, were born outside of Pelonomi. (See Table 5). In both studies teenage pregnancies proved to be a significant problem with more than 20% of mother's being less than 20 years old. Primigravidas again represented the majority of mothers and caesarean sections accounted for the largest proportion of deliveries in both studies. Male babies remained dominant at more than 60%.

In the 2007 study, Dr van der Vyver¹ looked at the person responsible for resuscitation of the infants with HIE compared to their outcome. She found that resuscitation by midwives yielded the highest percentages of deaths and neurologically abnormal infants at follow up. In the 2014 study, the question: "Resuscitated or not?" wasn't always asked, as this did not form part of the data form. The initial person treating the baby was seen as the "resuscitator" of the neonate. In the 2014 study most neurological abnormal infants were initially seen by midwives, but the majority of babies who passed away were referred by Medical Officers in the periphery. (See Table 6)

	2007				2014			
	<i>N</i>	Normal	Abnormal	Death	<i>N</i>	Normal	Abnormal	Death
Total	112	88	10	14	161	135	17	9
		78.6%	8.9%	12.5%		83.9%	10.6%	5.6%
Midwife	31	21	5	5	41	33	8	0
		67.7%	16.1%	16.1%		80.5%	19.5%	0.0%
Intern	20	17	2	1	26	25	0	1
		85.0%	10.0%	5.0%		96.2%	0.0%	3.8%
Registrar pediatrics	49	42	1	6	67	60	4	3
		85.7%	2.0%	12.2%		89.6%	6.0%	4.5%
Other	12	8	2	2	27	17	5	5
		66.7%	16.7%	16.7%		63.0%	18.5%	18.5%

Table 6. The outcome of infants diagnosed with HIE with regards to resuscitation by different groups of staff in the year 2007 and 2014.

*Other: 2007 study: Obstetrics and Gynaecology registrars, Medical officers, Unknown and paramedics, 2014 study: Obstetrics and Gynaecology registrars, Medical officers.

NOTE: Due to the small "n" of the Obstetrics and Gynaecology registrars, they were placed with 'other', but the group had a very large intra group variation.

Dr van der Vyver¹ found HIV infection, primiparity and meconium- stained amniotic fluid to be the most common maternal risk factors. There was a notable decline in HIV exposed babies with 59.8% of babies admitted with HIE being born to HIV infected mothers in 2007 vs only 21.25% in 2014. Meconium exposure remained a significant risk factor with prolonged labour being the third most common risk factor identified in 2014. (See Figure 3)

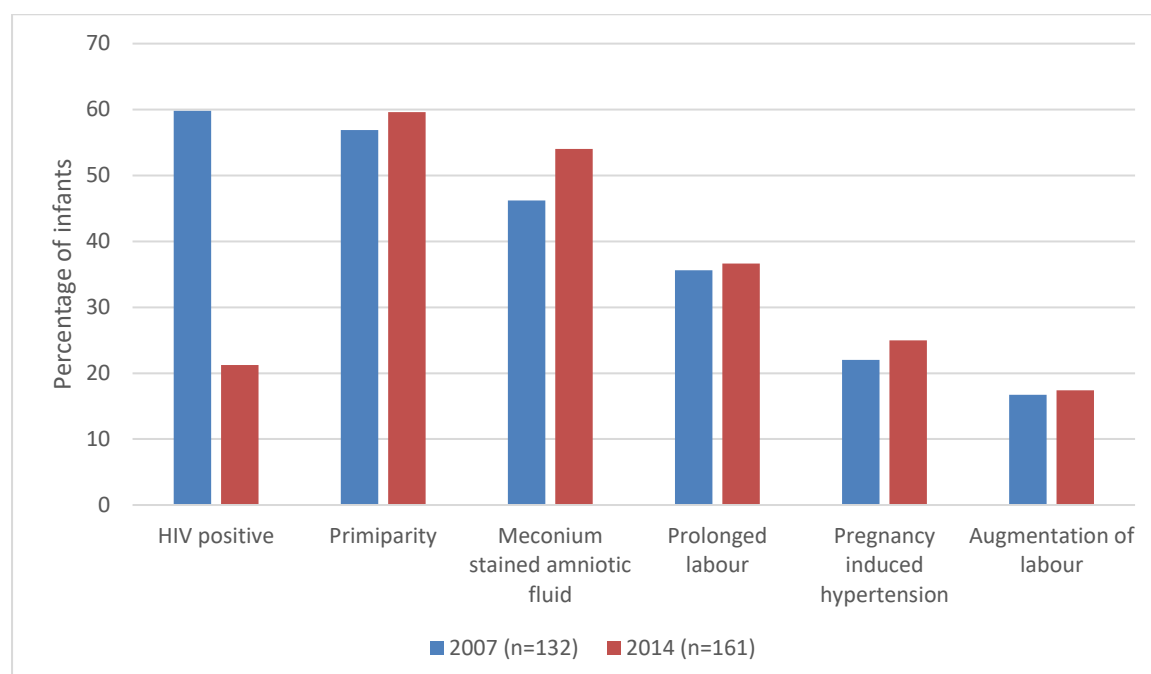


Figure 3. Comparing maternal risk factors associated with the diagnosis of HIE in neonates

The number of babies diagnosed with fetal distress before birth increased from 29.5% to 53.16% in 2014. (See Table 5). More than two hours delay before delivery remained the norm at 48.57% vs 43.6% in 2007.

The majority of infants were still diagnosed as having grade 1 HIE with a slight increase in grade 2 (33.3% vs 39.75% in 2014) and a slight decrease in grade 3 cases (12.1% vs 8.07% in 2014, see Table 5)

The wrongly classified grade 1 babies would have increased the number of grade 1 HIE in 2014 to 69.28% and decreased the percentage of grade 2 to 22.64% (a total of 17.11% were wrongly classified.) The grade of HIE with regards to outcome was again found to be statistically significant when combining the 2007 and 2014 data ($\chi^2=177.18$, $df=2$ and $p<0.001$). Only 27.6% of the infants diagnosed with grade 3 HIE in 2007 and 2014 combined, survived.

The number of babies classified as neurologically abnormal on follow up increased from 9.4% to 11.18% in 2014, although the increase was not statistically significant.

The deaths related to HIE decreased over the seven years to 5.59% from 11.4%. (See Table 5) The increased survival rate is of clinical significance, although it lacks statistical significance ($c2=3.22$, $df=1$, $p=0.07$).

Looking at the HIE-related deaths as a proportion of all deaths, it was calculated that HIE-related deaths had decreased from 16% of all neonatal mortalities in 2007 to 7.6% in 2014.

Booking late in pregnancy remained the number one patient-associated avoidable risk factor with no booking done in approximately 6% of cases. The most common medical personnel-associated factor was a delay in referring mothers which increased from 12.9% in 2007 to 16.77% in 2014. (See Table 7)

Missed cases of foetal distress and prolonged second stage of labour without intervention represented the second and third most cases in both time periods. Dr van der Vyver¹ found inadequate neonatal resuscitation as a factor in 9% of cases vs only 1.68% cases identified in 2014. (See Table 7)

A quarter of administrative-associated factors were still represented by inadequate theatre facilities (24.2% vs 25.47% in 2014). An association between inadequate theatre facilities and foetal distress ($\chi^2=11.8025$, $df=1$, $p=0.006$) was found when combining the data. Two thirds of patients that were deemed to be influenced by inadequate theatre facilities, developed foetal distress. (See Table 7)

Lack of transport was identified as the second most common factor in both studies with the percentage increasing from 15.9% to 21.74% on 2014. (See Table 7)

Table 7.

Comparison of top three avoidable risk factors identified in infants diagnosed with HIE in 2007 and 2014

2007 (n=132)			2014 (n=161)		
Avoidable risk factors	Number of cases	%	Avoidable risk factors	Number of cases	%
Patient-associated factors					
Booked late in pregnancy	41	31.1	Booked late in pregnancy	24	14.91
Never initiated antenatal care	8	6.1	Never initiated antenatal care	9	5.59
Delay in seeking medical attention during labour	7	5.3	Failed to return on prescribed date	9	5.59
Medical personnel-associated factors					
Delay in referring the patient for secondary/tertiary treatment	17	12.9	Delay in referring the patient for secondary/tertiary treatment	27	16.77
Inadequate neonatal resuscitation	12	9.1	Fetal distress not detected intrapartum, fetus monitored	10	6.21
Fetal distress not detected intrapartum, fetus not monitored	9	6.9	Management of 2 nd stage labour: prolonged with no intervention	10	6.21
Administrative-associated factors					
Inadequate theatre facilities	32	24.2	Inadequate theatre facilities	41	25.47
Lack of transport: institution to institution	21	15.9	Lack of transport: institution to institution	35	21.74
Insufficient doctors available to manage patient	13	9.9	Insufficient doctors available to manage patient	4	2.48

The median of the length of stay in the NHCU remained 6 days. The total patient days were 860 in 2007 compared to 1104 in 2014. In 2015 the number of babies admitted for more than 10 days almost tripled.

The patient days increased in 2014 as most of the patients remained 11-15 days in the unit, compared to the majority of patients staying 5 days or less in 2007. In the 2014 study the duration of stay proved to be statistically significant with regards to outcome ($\chi^2=11.8162$, $df=5$, $P_f=0.0181$) and neurological status at discharge ($\chi^2=26.0013$, $df=5$, $P_f=0.0002$), as would be suspected. The grade of HIE was not found to be statistically significant with regards to the duration of stay in the unit in 2007 ($\chi^2=3.5373$, $df=2$ and $P_f=0.1544$), but in 2014 it was significant ($\chi^2=12.0981$, $df=2$ and $p=0.0029$).

5. Discussion

In 2014, a total of 1527 babies were admitted to the Pelonomi Neonatal High Care Unit, almost 500 more compared to 2007. In total, 1500 more babies were born in 2014²⁵. This drastic increase in number of births and admissions is noted despite an unchanged number of beds available in the unit and with staff being more limited each year.

5.1 Staffing

According to the 2014/2015 SA Health Review the number of doctors working in the public health sector in the Free State has dropped from 716 in 2014 to 539 in 2015. The report also stated that the province lost 28 medical specialists in the same year. It is reported that the Free State has only 23.3 doctors per 100 000 patients. This information is sourced from the Personal and Salary Administration System (Persal).⁴⁴

The level of Nursing staff employed is also of concern. According to two Wits University Professors writing in the SA Health review, the number of professional nurses who are registered with the SA Nursing Council nationally is about 133 127, although only half of them (68 105) are working in the public sector. It is also estimated that by 2010, the health department staffing level was already short of 44 700 nurses, and it is reported that only 3 500 new nurses are trained every year.⁴⁵ Therefore a shortage of midwives can be expected and has been reported.⁴⁶ The latter directly influences monitoring and care of mothers and newborns. The availability of skilled birth attendants is of utmost importance to improve perinatal outcome measures.^{47,48,49} Multiple studies have highlighted an increased risk for asphyxia with a lack of professional help at birth.^{17,50}

5.2 Maternal risk factors

5.2.1 Parity

Primiparity was identified as the most common maternal risk factor. In a study done in Sweden it was found that 68% of asphyxiated babies were born to primigravida mothers.⁵¹ According to a study done in Nepal, primiparous women carried a higher risk for birth asphyxia mortality.⁵²

5.2.2 Maternal age

Young maternal age has been linked with an increased risk for neonatal mortality.⁵³ In 2008 18.9% of Free State girls between the ages of 15-19 answered 'Yes' to a survey question: "Have you ever given birth?" compared to 14.6% as an average in South Africa.⁵⁴ A Love Life impact study done in SA in 2011 found that 19.2% of this same age group reported to have been pregnant at least once.⁵⁵ This data underlies the concern that about a quarter of infants included in the 2007 (24.2%) and 2014 (22.98%) studies, were born to teenage mothers. The overall percentage of teenage mothers were 17.7% in the Free State and 14.2% in Pelonomi for the year 2014²⁵.

Literature supports the fact that young maternal age should be regarded as a possible increased risk for HIE.^{17,52,56} Extremes of maternal age have been associated with deaths due to intrapartum asphyxia.⁵⁷ It is therefore important to highlight the fact that in our specific population 30-33 year old woman had a higher risk compared to women >35 years of age.

5.2.3 Anaemia

Almost a third of mothers were found to be anaemic in the 2014 study. The total number might even be more as another third of mothers' files and/or information were not available. Anaemia is a risk factor that is easily correctable. Care must be taken that all pregnant women are screened for anaemia at follow up.

A study done in Pakistan found 60% of mothers included in a birth asphyxia study to be anaemic.¹⁷

The fact that logistical regression identified anaemia to be a possible predictor of a lower grade of HIE might be due to the fact that the mothers may have been more closely followed and monitored during their pregnancy, as with the case of pre-eclampsia that was also identified as a possible indicator for a lower grade of HIE (even while these might be predictors of the occurrence of HIE in and of themselves—something which could not be tested given the current scope of this study).

5.2.4 HIV status of the mother

Dr van der Vyver found 59.9% of mothers included in her study to be HIV+, making it the most common maternal risk factor associated with HIE. This is in stark contrast to the 2014 study, where only 21.25% tested positive. An association between HIV positive mothers and perinatal death from intrapartum hypoxia was found in a South African study done in 2006 to 2008 in southwest Tshwane.⁵⁸ The prevalence of HIV in the Free State has been staying relatively steady at 29.8% in 2013, 32% in 2012 and 32.5% in 2011.⁵⁹ Research information about the the role of HIV exposure of infants and the risk of HIE is inadequate.

According to the 2012 South African National HIV Prevalence, Incidence and Behaviour Survey, almost a quarter of all new HIV infections occurred in females aged 15-24, but it also reported that there was a decline in HIV incidence among the same age group from 5.3% in 2002-2005 to 2.1% from 2008-2012.

The incidence rate of 4.5% under black African females aged 20-34, is the highest recorded incidence among all the analysed population groups. The epidemiological curve has shifted since 2008 from the 25-29 year age group, with HIV prevalence peaking at 30-34 year age group for females. The 2012 results showed that HIV prevalence is higher than the general population in African females 20-34 years of age.⁶⁰ This is also the main age for childbearing.

The WHO recommends that HIV testing should have a sensitivity of at least 99% and a specificity of at least 98%.⁶¹

In 2010 the South African government conducted a study in Cape Town's local clinics. It concluded that the rapid HIV test averaged only a 68.7% sensitivity, and thus is missing nearly a third of positive patients. This was thoroughly investigated and poor testing methods were found. After quality improvement measures were implemented, sensitivity rose to 95.1%.⁶² Correct utilization of rapid tests are incredibly important and need to be enforced and challenged on a regular basis.

5.3 Gender of the babies:

It is a well-researched fact that male gender of the neonate has been red-flagged as a risk factor for HIE.^{17,50,63,64} According to Johnston et al, female sex hormones have a possible protective effect against ischemia.⁶⁵ Our studies agree with these findings as approximately two thirds of the HIE cases, in both studies, were male infants.

5.4 Meconium exposure

Meconium exposure has been identified as a risk factor in multiple hospital based studies.^{17,18,21} Meconium exposure with or without aspiration increased from 49.2% in 2007 to 54.04% in 2014, although the increase was not statistically significant (4.8% increase with a 95% CI of -6.8%–16.3%). This remains worrisome as it indicates that more babies are developing foetal distress. The cause for increase should be thoroughly investigated.

One possible contributing factor is that the percentage of babies having a delay in the time of delivery from time of the diagnosis of foetal distress has also increased.

5.5 PIPP factors identified

5.5.1 Foetal distress

The number of babies diagnosed with foetal distress prior to delivery almost doubled. It is questionable whether foetal distress was more often missed in 2007 or if the delay in delivering potentially vulnerable neonates led to the increase of babies developing foetal distress.

The question can also be asked if the CTG's were correctly interpreted. CTG's were not routinely examined as they were not always available. This yields another research opportunity.

Suboptimal care is a world-wide problem^{66,67,68} and every case has to be individually investigated. A study done in Cape Town by Fawcus et al, noted that in 51% of infants with neonatal encephalopathy, absent or no monitoring of the foetal heart was done.⁶⁹

Jonsson et al looked at the association between cardiotocographic (CTG) patterns and neonatal outcome and found that an abnormal admission CTG pattern indicates a poorer outcome and is more often associated with pathologic CTG patterns preceding delivery.⁷⁰ A study published in the American Journal of Obstetrics & Gynaecology found that electronic foetal heart monitoring has a low predictive power in identifying neonates with metabolic acidosis and HIE.⁷¹ Failure to detect or respond to foetal distress, using whichever method available, is an urgent matter that needs to be addressed.⁷²

Saving Babies 2000 survey of perinatal deaths at 27 hospitals, reported that 43% of deaths were due to inadequate foetal monitoring and 19% followed failure of a health worker to respond to poor labour progression^{13,73} and current data unfortunately confirms these challenges.¹⁵ As CTG monitoring is the main method of monitoring of foetal wellbeing in the current setting, it should be available in all clinics and hospitals. In only three cases "No CTG paper available" was identified as an administrative avoidable factor while "load shedding" was attributed to one case where monitoring could not be done.

Optimal monitoring need not be expensive. A study done to look at obstetric care in low-resource settings used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) System to assess evidence quality and to make recommendations. They recommend against using cardiotocography in settings without safe theatre facilities for caesarean sections. Intermittent auscultation with a Pinard stethoscope to detect baseline heart rate as well as early or late heart decelerations was strongly recommended, but still requires more evidence. The use of a simplified umbilical artery Doppler is strongly recommended but requires more research into developing a low cost device. A robust hand-held doptone using wind-up technology rather than batteries has been developed for use in low-resource settings.⁷⁴ A trial in Zimbabwe found that the use of intermittent hand-held doppler when compared with continuous cardiotocography, led to similar rates of caesarean delivery (28% vs 24%) and comparable foetal outcomes.⁷⁵ An important research gap has been identified and needs urgent attention.

5.5.2 Prolonged labour

Prolonged labour remains one of the top three maternal risk factors. A possible reason for this can be found by looking closer at the PIPP factors.

5.5.2.1 Delay in referring to secondary hospital

A delay in referring patients for secondary treatment was identified as the most common preventable personnel associated factor in 2014 and second most preventable factor in 2007. It was also noted as one of the top five avoidable factors in a national South African study.¹²

5.5.2.2 Management of active labour

Incorrect management of the 2nd stage of labour was also identified in both studies. Both showed a delay in intervention with prolonged labour.

Fawcus et al, as mentioned above, also determined prolonged second stage of labour to be the greatest obstetric risk factor (odds ratio 11.96; confidence interval 2.93-56.4).⁶⁹ Prolonged labour should be a warning to monitor for asphyxia and possible HIE as multiple other studies have flagged it as a risk factor.^{22,23,76}

Incorrect and inadequate partogram usage was once again identified as one of the top 5 personnel associated avoidable factors in both 2007 and 2014's studies and goes hand in hand with the incorrect management of stage 2 labour. A Cochrane review found a nonsignificant reduction in risk of Caesarean delivery with partogram usage, but higher income as well as low income settings were taken into account.⁷⁷

Research done in low-resource settings highly recommend the usage of the partogram for monitoring of mother and baby in labour as it can serve as a guide for timely referral to emergency facilities.⁷⁴ A large prospective study done by the WHO in South-East Asia found that partogram usage was associated with a reduction in emergency caesarean sections, decrease in need for augmentation of labour, stillbirths and a reduction in prolonged labour.⁷⁸ One needs to take staffing levels and availability of theatre time into account when assessing the quality of monitoring.

5.5.2.3 Delay in access to obstetric care

In women with obstetrics emergencies, ‘three delays’^{38,79} have been identified with regards to access to care: (1) delay in the decision to seek care (due to cultural beliefs, family influences, poor recognition of problems in pregnancy or labour), (2) delay in reaching a health facility (due to transport issues, road infrastructure, distance etc.), (3) delay in receiving quality care (poor training, inadequate equipment, clinical algorithms).

The ‘Saving Babies 2000’ survey, as mentioned above, reported that 37% of perinatal deaths occurred because of a delay in women presenting to health institutions.^{13,73}

Confidential enquiries into HIE in South Africa 2009’s audit found that a number of intrapartum-related deaths were associated with mother’s delaying to seek help during labour.²⁶ The current studies at hand also identified this issue as one of the top three avoidable patient associated factors.¹

The ‘second delay’ (delay in reaching a facility) presents a major issue. It has made headlines in the news on multiple occasions.^{80,81}

Lack of transport from institution to institution was identified as the second most common administrative avoidable factor in both the 2007 and 2014 studies. Most of the ambulances has been outsourced to a private company, Buthelezi Ambulance Services. They have to cover a vast area with limited staff, equipment and ambulances. Patients cannot afford private transportation. Unfortunately we know that the risk of neonatal deaths and intrapartum related stillbirths are much higher in poorer and lower-income countries.^{3,36} The question could be asked how big of a role lack of transport plays in the outcome of these mothers and babies.

Multiple strategies to link mothers to health care facilities have been studied and must be applied as best possible in our setting.⁸² Maternity waiting homes, task shifting, community referral, transport schemes and financial strategies are a few examples to explore and develop.⁸³ This will take joint effort from the health workers and government.

One of the biggest concerns identified is a lack of adequate theatre facilities in Pelonomi Hospital. With the current patient load, one theatre for gynecological and obstetric cases, especially after hours, is not sufficient. In the Southern Free State, after hours emergency caesarean section facilities are only available at Bothshabelo, Thaba Nchu or Pelonomi hospital. At the time of this study, the vast Xhariep district did not have a single after hour’s theatre service available. These facts shed light on the worrying number of emergency caesarean sections being done. Emergency caesarean sections are associated with a high risk of newborn encephalopathy, while elective caesarean sections has an inverse association.⁸⁴ The delay in timely caesarean delivery due to a shortage of ambulance services and theatres are causing foetal hypoxic injury.^{39,85} As approximately 60% of babies included in both the 2007 and 2014 studies were delivered by Caesarean section, it is stressed again that this is a matter that needs to be firmly addressed. Literature confirms the fact that these high risk patients are usually delivered by caesarean section.^{24,76,86}

5.5.3 Clinic bookings

The fact that the number of mothers booking late in pregnancy (after 20 weeks gestation) remained the most common patient avoidable factor and that there is still a large amount of mothers who present completely unbooked, is of great concern. Early booking and identification of high risk pregnancies are essential. Absence or poor-attendance of antenatal care has been identified as a risk factor for "birth asphyxia" in many developing countries.⁵⁰ A study looking at risk factors for asphyxia done by Majeed et al found that 64% of women included in the study never initiated antenatal care.¹⁷

Shaheen compared perinatal mortality in booked and unbooked cases. The perinatal mortality rate was found to be 111/1000 live births in unbooked cases compared to 17/1000 in booked cases.⁸⁷ The question needs to be asked if poor booking and follow up can be better explained by a lack of access to healthcare facilities.

5.6 Time of delivery

Interesting studies have been done regarding time of delivery as a risk factor, as hospitals in general are relatively poorly staffed at night. It was found that lower Apgar scores were recorded at night and that the rates of perinatal- and neonatal mortality are higher compared to daytime rates.^{66,88,89,90} Studies comparing weekday vs weekend outcomes are less certain.^{88,91,92} In the 2007 study 73% of HIE patients were admitted after hours with 79% in 2014.

5.7 Grading of HIE and outcome

Grade one HIE was by far the most common grade of ischemia noted, secondly grade two and lastly grade 3. These findings correspond with findings in the literature.¹⁷ The fact that 17.11% of grade 2 neonates were wrongly classified as grade 1, is worrisome.

The corrected percentages of grade 1 and 2 agree more with Dr van der Vyver's study, showing that the adjustments that were made, probably are correct. Therefore multiple opportunities were missed to cool grade 2 HIE infants, as they all should qualify for cooling. These neonates were also missed to follow up, as only grade 2 and 3 HIE babies are booked at our high risk clinic.

A study done in Sweden looked at the long term neurodevelopmental outcome of neonates diagnosed as Moderate HIE. These babies were all born in 1985 and were followed up until 15-19 year of age. The study found that 81% of patients had cognitive dysfunction, with or without other impairments such as Cerebral Palsy.⁶⁸

Other studies also reported that survivors of moderate encephalopathy had definite handicap with regards to scholastic performance and even behavioural problems.^{43,93,94}

Pin et al found that all grade 1 infants had normal neurological sequela, while 32% of grade 2 and almost 100% of grade 3 presented with adverse outcomes.⁴³

According to a neonatal symposium published in the Paediatrics and Child health in 2014, HIE accounts for 30% of cerebral palsy cases and 15-20% of infants deaths in the post-natal period with 25% developing permanent and severe neuropsychological sequelae (mental retardation, visual impairment, epilepsy and hyperactivity).⁹⁵ It is estimated that intrapartum hypoxic ischemia at term causes about 80% of all cases of dyskinetic CP.⁹⁶

In the 2014 study, three grade 1 HIE neonates were reported to have abnormal neurological features at follow up, two of these patients were referred from clinics. The question could be asked if they were also missed grade 2 HIE patients. Out of all the patients reported as “neurological abnormal” at follow up, fifteen (68.18%, n=22) were classified as grade 2 and three (13.6%) as grade 3. As mentioned with the results, defaulting during follow up remains a big challenge.

The fact that five patients who were reported to have “normal” neurological features at discharge, were classified as “abnormal” on follow up, stresses the importance of evaluation these patients in the long term.

The number of HIE related deaths decreased by approximately 6% in our two comparing studies. The percentage of HIE deaths in relation to total neonatal mortalities also decreased with 9%. These figures have to be interpreted with other background factors in mind e.g. many HIE 3 cases are not being accepted from peripheral hospitals due to poor prognosis and limited space at Pelonomi. Ineffective transport, late referrals and a collapsing referral system could all play a role in the very ill patients not reaching our facility in time.

5.8 HIE and seizures

Seizures were noted in more than half (59%) of the babies that were classified as “neurologically abnormal” at follow up in the 2014 study. In both the 2007 and 2014 studies, about 20% of infants presented with seizures. In a neonate who presents with convulsions in the first week of life, the most frequent etiology is HIE (30%).⁹⁷ HIE is furthermore said to cause 50-60% of all newborn convulsions.^{98,99} Human and animal studies suggested that neonatal seizures can lead to worsened brain injury, and that it can decrease the threshold for further seizures and that long term neurological outcome is adversely affected.^{100,101} In contrast, another study found that moderate HIE not to be associated with post-neonatal epilepsy.¹⁰²

The time of the seizure seems to be important as Graham et al found that asphyxiated neonates presenting with seizures within the first 24h were significantly more handicapped compared to those presenting with seizures after 24h.¹⁰³ Primiparity, evidence of foetal distress and male sex were noted among risk factors for neonatal seizures.^{104,105}

5.9 HIE and glucose abnormalities

5.9.1 Hypoglycaemia

Another interesting finding from the 2014 study was that 27.33% of neonates presented with hypoglycaemia in the first 24 hours. Possible contributing factors to keep in mind is a delay in admitting these often very sick patients post resuscitation and fluid restriction as part of the protocol of treating term infants with HIE.

Asphyxia is an important cause of hypoglycaemia as glucose is rapidly metabolized anaerobically in an attempt to minimize cellular energy depletion in all tissues, including the brain.¹⁰⁶ A study done in Dallas looked at initial hypoglycaemia and brain injury in term infants with severe foetal academia.¹⁰⁷

It was found that there was an 18.5-fold risk increase for brain injury with initial hypoglycaemia, particular in depressed term infants who required resuscitation and infants presenting with severe academia. They proposed a follow up study to look at early glucose replacement in high risk infants with initial hypoglycaemia and the impact on subsequent brain injury.

A higher severity of encephalopathy and a worse outcome at 2 years of age are associated with HIE neonates compromised by hypoglycaemia.⁹⁵ In an infant with neonatal encephalopathy, hypoglycaemia should be avoided at any time and at all cost.¹⁰⁸ Further research in the management and prevention of hypoglycaemia in HIE is proposed.

5.9.2 Hyperglycaemia

In a new finding in 2014 hyperglycaemia was found to be significant with regards to outcome and neurological status at discharge. Hyperglycaemia induces increased production of lactic acid in tissues and can therefore cause derangement of pH homeostasis.^{109,110} In adult experimental models it was founds that hyperglycaemia worsen neuronal injury after a hypoxic incident, but the same results were not found in immature animals.¹¹¹ This is likely explained by maturation differences in the rate of cerebral uptake and metabolism of glucose.¹¹² The fact that hyperglycaemia was identified as such a positive predictor of worse HIE grading leads to the question of whether hyperglycaemia needs to be treated more aggressively to prevent neurological sequelae? Hyperglycaemia can also cause haemorrhage by having a hyperosmolar effect. Maintaining glucose within normal ranges is thus of utmost importance.¹¹³

5.10 Prevention and management of HIE

Dr van der Vyver initiated an intensive resuscitation training program for all the Pelonomi staff and referring hospitals after her study findings. With the results of the 2014 study in mind, it is confirmed again that resuscitation needs to be a daily part of training. “Helping babies breathe” (HBB) is a simplified neonatal resuscitation program, initiated by the American Academy of Paediatrics in 2010. This program was specifically developed for the limited resource setting.¹¹⁴ District master trainers and staff in the Free State and nationally have received training in this program from 2015. Ideally, HBB drills should be done every morning.

Thirty percent of intrapartum-related neonatal deaths can be prevented by facility based neonatal resuscitation training – this startling fact was demonstrated in a recent systematic review and meta-analysis by Wall et al.¹¹⁵ When it comes to cost-effectiveness, resuscitation is regarded as being the most cost-effective of all child health interventions.⁴⁸ Therefore proper time and funding resources should be utilized with regards to adequate resuscitation training.

Emergency obstetric care training courses have been proven to reduce the incidence of neonatal encephalopathy and low 5 minute Apgar scores.¹¹⁶ Obstetric drills and simulations are strongly recommended according to latest research.⁷³

As intrapartum-related mortality and morbidity is such a complex issue with scanty evidence with regards to management and prevention¹¹⁷, quality research is of the utmost importance. The WHO undertook the “Saving Newborn lives” initiative in 2005 to review global estimates of birth asphyxia³⁶ and has also called for an expert meeting¹¹⁸. Research priorities to reduce deaths due to asphyxia have been investigated¹¹⁹ and has the potential to prevent almost one million unnecessary deaths each year.¹²⁰

Multiple strategies have been investigated in an attempt to prevent avoidable neonatal deaths.

Intrauterine resuscitation is strongly recommended⁷⁴ and advised by the American College of Obstetrics and Gynaecology (ACOG) while awaiting emergency caesarean section to reduce intrapartum related adverse outcomes¹²¹ and was proven to lower the risk on NICU admissions.⁷² Unfortunately not much can be said about in-utero resuscitation in our own setting as maternal files contained insufficient notes regarding the matter.

Auditing of all cases of mortality is essential¹²² and have been proven to reduce deaths¹²³ and improve suboptimal care¹²⁴. Audit has also been found to be effective in South Africa with studies done in the Eastern Cape¹²⁵ and Kwazulu-Natal¹²⁶, both showing a significant decrease in perinatal mortality. Buchmann et al proposed a check-list for confidential enquiry into HIE while simultaneously incorporating the PIPP audit guidelines for elements of suboptimal care.²⁶ Auditing can provide vital information with regards to prevention of intrapartum-related deaths and should be implemented without exception.

A study done in the UK over a 12 year period proved that intrapartum asphyxia may be preventable by reducing all grades of Hypoxic-ischemic encephalopathy from 2.41 to 0.77/1000 live births ($P < 0.001$).¹⁴ Velaphi and Pattison deemed a third of intrapartum related deaths in South Africa, during the period 1999-2003, to be preventable.¹²

By using protocols and uniform approaches, the Hospital Corporation of America, the largest private health care facility in America, managed to dramatically decrease malpractice claims, caesarean section rates and overall adverse outcomes of mothers and babies.¹²⁷

Other proven strategies to decrease neonatal mortality include continuous social support during pregnancy and labour^{128,129} and task shifting^{130,131} by maximizing resources through the redistribution of specific tasks from senior qualified professionals to capable but less specialized personnel who can still perform the task safely.

Safety checklists have proven to be effective and is currently recommended.⁷⁴ The WHO has been working on a “Safe Childbirth Checklist” which has shown improvement of maternal and newborn care in pilot settings¹³² and is currently being implemented nationally¹³³. The results of this study was used to give suggestions to a task team put together to revise the Maternal Case Record books in the Free State. In March 2016 meetings were under way and a suggested “Asphyxia screening tool” was put together for further development. The idea is to identify patients at risk for asphyxia and to refer them to a high risk clinic at an appropriate gestation or to ensure early transfer to maternal waiting homes.

All preventative strategies are aimed at improving the outcome of mother and child and decreasing hospitalisation. The number of days spent in the NHCU increased in 2014 compared to 2007 and in 2007 the total amount of expenditure for Pelonomi Hospital was already estimated to over a million rand. This accentuates the ever increasing financial burden of HIE on the health system.

Moderate hypothermia initiated within 6 hours post a hypoxic incident remains the mainstay treatment of grade 2 HIE and has been proven to improve survival without disability or cerebral palsy by 40% and to reduce neurological disability by almost 30%.¹³⁴

Multiple trials have supported the positive neurological outcome^{135, 136} with the most recent being the TOBY (Total Body Hypothermia for Neonatal Encephalopathy Trial) study group.¹³⁷

A cooling facility has only been available in Universitas hospital from 2009. Due to mechanical problems and financial constraints few patients were given the opportunity of cooling in 2014.

A search for treatment to augment neuroprotection and neuro-restoration is currently underway. Possible strategies include anti excitatory or anticonvulsants e.g. Magnesium.¹³⁸ A small study done in Romania explored the neuroprotective effects of high dose phenobarbitone and erythropoietin and a positive influence on the outcome of newborns with perinatal asphyxia was found.¹³⁹ Bigger studies are however necessary.

Other strategies include inhibitors of nitric oxide production¹⁴⁰, Calcium channel blockers¹⁴¹ and growth factors.¹⁴²

Exciting work is being done regarding epigenetic programming and its role in hypoxia related injuries.¹⁴³

The focus therefore needs to be on identifying infants at highest risk for developing hypoxic ischemic encephalopathy.¹⁴⁴

Many research opportunities have been identified with regards to the prevention and management of intrapartum asphyxia, yet research funding remains limited at national and international level.¹⁴⁵ Detailed policies and specific national goals focusing on intrapartum asphyxia need to be developed and implemented in South Africa.¹⁴⁶

Without more attention to improve care and to emphasize birth asphyxia research, the prevention of 1 million intrapartum related deaths will remain out of our reach.⁴⁷

Urgent further research is required to decrease morbidity and mortality associated with HIE.

6. Shortcomings of the study

All retrospective studies are hampered by omissions, accuracy, as well as lost data.

The fact that 17 cases, 6 maternal and 11 neonatal cases, were excluded due to unavailable or incomplete information need to be taken into account. Thirty seven maternal files could not be found and 14 were not available. The unavailable files were mostly from patients referred from a clinic or another hospital. Insufficient notes were also more likely to be found with referred patients compared to Pelonomi born patients. The fact that 30% of the maternal files for admitted Pelonomi mothers were missing, is of great concern.

7. Conclusions and recommendations

“Are we doing better?” I will list a few pointers and recommendations which arise from our findings and discussion;

1. *HIE, although mostly preventable, remains a major burden in South African hospitals, including Pelonomi Hospital.*
2. *The place of delivery (in- or outside of Pelonomi) influenced the outcome of babies and also the neurological status prior to discharge. The grade of HIE with regard to place of delivery was significant, therefore high risk mothers have to be identified and must deliver in secondary or tertiary hospitals. Well-functioning maternity waiting homes need to be established with urgency.*
3. *The outcome and neurological status at discharge with regards to the resuscitator was statistically significant with medical officers at outside hospital settings did fare poorly. Resuscitation training is now compulsory for all medical personnel and needs to be evaluated regularly.*
4. *A higher grade of HIE correlates with a worse outcome and neurological outcome.*
5. *The more anticonvulsants a neonate required, the worse the outcome and neurological status at discharge.*
6. *Hyperglycaemia emerged as a possible factor associated with a higher grade of HIE and may be an appropriate target for treatment.*
7. *Anaemia and Pre-eclampsia was identified as possible “protective” factors and were associated with a lower grade of HIE, but that finding may be spurious as it may be a surrogate marker for better maternal care.*
8. *Compared with the first study, there was a sharp decline in HIV positive mothers with HIE babies. Primiparity, meconium aspiration and prolonged labour remain some of the most common maternal associated risk factors and should raise awareness for possible HIE.*
9. *Unbooked mothers and mothers who book late in pregnancy are a risk factor and this need to be firmly addressed at different levels, e.g. through education programmes at school in the subject Life Orientation, local radio and television and awareness campaigns.*
10. *Preventing teenage pregnancies and flagging teenagers as high risk pregnancies for HIE can positively influence pregnancy outcome.*
11. *Delay in referral of patients was identified as a major preventable factor in most cases. Medical personnel need to know when to refer and how to identify high risk patients for HIE.*
12. *Correct diagnosis of foetal distress and partogram usage are factors that require urgent attention.*
13. *Inadequate theatre facilities were identified as the number one preventable administrative factor and was associated with foetal distress.*
14. *Lack of adequate transport to medical facilities is a matter for urgent attention.*
15. *The fact that the HIE classification was wrong in an significant number of babies, needs to be addressed as this directly influences management and follow up of the neonates.*
16. *Although there was a 6% decrease in deaths between the two studies, the fact that neurological outcome was worse in 2014 remains worrisome.*
17. *The number of patients requiring care for more than 10 days almost tripled in 2014 and accentuates the burden of HIE on the health care system as longer stay was also associated with worse outcome.*
18. *Further research and funding for HIE is a must*
19. ***Are we doing better?” If we look at our results, and the comparison between the two time periods, the answer may be a rather unfortunate “not yet”.***
20. ***This should motivate us to implement and monitor these recommendations, repeating the study in seven years in the hope of a resounding “yes”.***

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