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OUTCOME FOLLOWING ASPHYXIAL INSULT IN TERM NEONATES

L.G. Scher

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ABSTRACT

The admission records of all newborns admitted to the Johannesburg Neonatal Intensive Care Unit over a four year period with a birthweight ≥2000 grams and who were asphyxiated at birth and required ventilation were reviewed. Follow-up data were obtained from the Neonatal Follow-up Clinic files.

Of the 109 newborns who fulfilled entry criteria, 73 (70%) were males, 36 (30%) females. The mean gestational age was 36 weeks (± 2,9), mean birthweight 2700g (± 555). Apgar score at 1 minute was 1-2 in 33% of the patients, 3-4 in 33% and 5-6 in the remaining 33%. Outcome was normal in 44 (40%), death occurred in 16 (15%) and neurological deficit was found in 6 (6%). Forty three (39%) were lost to follow up.

It was shown that in subjects available for follow-up, seizures and cardiorespiratory complications of asphyxia (congestive cardiac failure/ tricuspid incompetence/ meconium aspiration syndrome/ persistent fetal circulation) were significantly associated with death or poor neurological outcome, whereas asphyxia (even requiring ventilation) without the latter signs and symptoms was predictive of good recovery.

DECLARATION

I hereby declare that this Research Report is my own unaided work. It is being submitted in partial fulfilment for the Degree of Master of Medicine in Paediatrics to the University of Witwatersrand, Johannesburg. It has not been submitted for any other purpose in the past.

Signed:

L. G. Scher

_____ day of _____ 2000.

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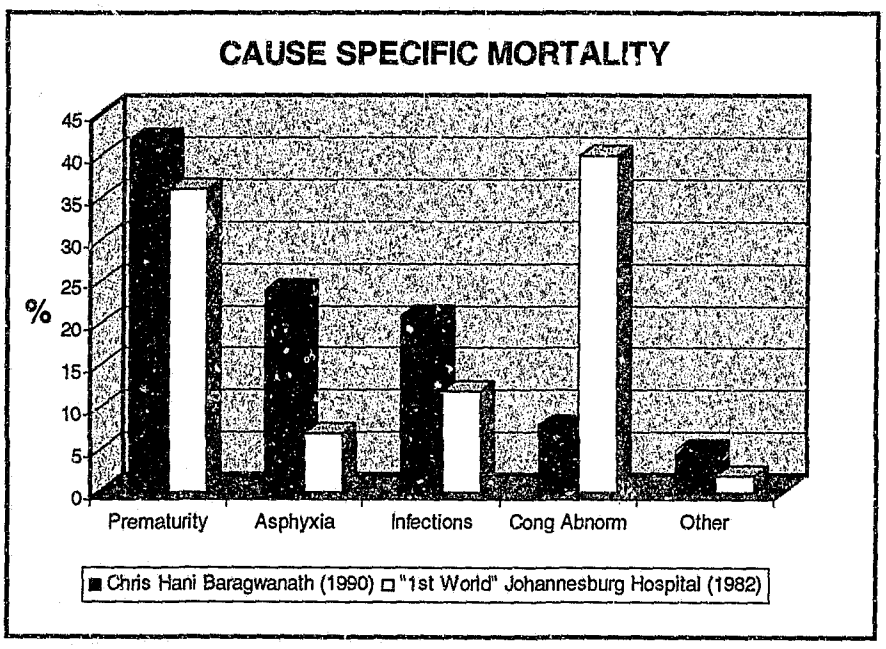
My grateful thanks and appreciation also go to Prof John Pettifor, Dr Ella Hartman and Dr John Rodda for all their support, encouragement and faith in me.

INTRODUCTION

Birth asphyxia is the end result of reduced oxygen and nutrient supply to the fetal brain with resultant metabolic and respiratory acidosis (1). Severe hypoxia or ischaemic insult to the fetus can manifest in the newborn as an encephalopathy and may result in neonatal death or in permanent motor and mental handicap, whereas milder insults may be of little consequence (2). Perinatal asphyxia continues to be a focus of research for clinicians interested in the prevention of brain damage, and animal experiments and clinical observations indicate a spectrum of damage following perinatal asphyxia, with such damage varying in both degree and in type (3).

In Britain, approximately one full-term baby per thousand dies or is disabled as a result of birth asphyxia (4), whereas in South Africa birth asphyxia remains a major cause of morbidity and mortality. At Chris Hani Baragwanath Hospital, 20% of all neonatal deaths are due to asphyxia (5,6). The following graph (Figure 1) shows the causes of mortality in neonates at Baragwanath Hospital in 1990 (Cooper P.A.; personal communication) as compared to Johannesburg Hospital in 1982 (7).

Figure 1



Wild studied a group of 25 term asphyxiated infants admitted to the Johannesburg Hospital Neonatal Unit between September 1980 and March 1982 (8). The mortality was 20%, and 16% were handicapped at the 2-year assessment. Twenty percent of the patients were lost to follow-up. The infants who died or were handicapped had lower Apgar scores at birth than normal infants. Infants lost to follow-up had significantly higher Apgar scores than those who died or were handicapped, suggesting a better outcome and lack of perceived need to continue visits to the Neonatal Follow-up Clinic.

In 1862, William John Little, an orthopaedic surgeon in London, described 47 children with what he termed spastic rigidity. He concluded that virtually nothing other than abnormalities at the time of birth could cause this clinical picture (9). However, in 1897, Sigmund Freud provided a contrasting view when he argued that "the anomaly of the birth process, rather than being the causal aetiologic factor, may itself be the consequence of real prenatal pathology" (10).

Almost a century later, Nelson and Ellenberg showed a poor correlation between the presence of cerebral palsy and the occurrence of birth asphyxia (11). They asserted that asphyxia must be severe to be associated with a substantially heightened risk of cerebral palsy, and observed that it was not obvious that preventing asphyxia would prevent an unfavourable neurological outcome (12). They also noted that mild or brief intrapartum asphyxia does not necessarily produce permanent brain damage, and only severe and prolonged isolated intrapartum asphyxia is associated with a substantial risk of cerebral palsy. Such a degree and duration of asphyxia is very uncommon, and when it occurs the usual outcome is either death or clinically normal development. Only a small percentage of survivors of this severe degree of asphyxia manifest clinically evident long-term neurological handicap (13).

The brain is not the only organ to be affected by asphyxia; evidence of multi-organ hypoxic-ischaemic injury can be documented during the first days of life in most newborns who have suffered sufficient intrauterine damage to affect the brain. The pathophysiology of the non-brain injury is probably due to the early shunting of blood flow away from these organs (14).

In a study by Perlman in which he reviewed the systemic manifestations of perinatal asphyxia in the term newborn infant, the presence of persistent oliguria was invariably associated with a significant neurological deficit and was a useful marker of poor long-term neurological outcome (15). He was unable to demonstrate a relationship between measures of fetal hypoxia (fetal heart rate abnormalities, arterial blood-gas measurement, Apgar score) and long-term neurological outcome. In his study, not

even hypoxic-ischaemic encephalopathy with seizures predicted an adverse neurological outcome.

This research project was therefore undertaken as a follow-up to the earlier study (8) to assess what changes might have taken place at the Johannesburg Hospital over the ten-year period and more specifically to:

1. study the short-term complications and the long-term neurological outcome of a group of newborns with a birth weight equal to or more than 2000 grams, a diagnosis of birth asphyxia, and who required ventilation. (This restriction to neonates ≥2000 grams largely excluded growth-retarded neonates and preterm infants, both of which are subject to damage independent of birth asphyxia.)
2. identify factors associated with adverse outcome.

METHODS

The computerised admission records of all patients admitted to the Johannesburg Hospital Neonatal Intensive Care Unit (NICU) over a four-year period were reviewed. Babies with a birth weight of ≥ 2000 grams were studied to exclude the effects of obvious chronic intrauterine growth retardation and very low birth weight on morbidity and mortality.

Only babies requiring assisted ventilation were included in order to restrict the study to the most severely asphyxiated infants i.e. those with respiratory compromise. Gestational age was assessed using maternal dates and the Ballard score (16). Follow-up data were obtained from the records and files of the Neonatal Follow-up Clinic. At this Clinic, patients are seen by a Paediatrician, Physiotherapist, Speech and Hearing Therapist and an Occupational Therapist.

1. *STUDY POPULATION*

This included infants with all of the following:

1.1. Birth weight ≥ 2000 grams.

1.2. Diagnosis of birth asphyxia as defined by a one minute Apgar score ≤6.

Although a one minute Apgar score of ≤6 may not be considered diagnostic of birth asphyxia, this criterion was chosen as it had been noted previously in a study by Rothberg et al that labour ward staff tended to overestimate Apgar scores (17). Therefore, this Apgar score, in combination with ventilation requirements, was used as the criterion for birth asphyxia.

1.3. A ventilation requirement within the first 24 hours of birth. This was defined by

one or more of the following:

a) FiO2 ≥0,6 with paO2 ≤50mmHg

b) PaCO2 >55mmHg

c) PH <7.25

d) Apnoea

2. *EXCLUSION CRITERIA*

Babies with the following problems were excluded from the study to eliminate other primary or secondary causes of central nervous system (CNS) dysfunction:

2.1. Chromosomal abnormalities

2.2. Obvious congenital abnormalities of the CNS

2.3. Congenital heart disease

2.4. Diaphragmatic hernia

2.5. Congenital infections

2.6. Neonatal meningitis

2.7. Inborn errors of metabolism

3. *PATIENT DATA*

The following data were collected on each patient:

3.1. Birth weight

3.2. Gestational age

3.3. Apgar scores at 1 and 5 minutes after birth

3.4. Presentation at delivery (vertex, breech etc.)

3.5. Mode of delivery

3.6. Duration of ventilation

In addition, the following 'Co-morbid' and/or 'symptomatic' neonatal problems were recorded:

3.7 Co-morbid:

3.7.1 Hyaline membrane disease (HMD) - defined by respiratory distress and conventional radiological changes of HMD

3.7.2 Pneumonia - defined by respiratory distress with radiological changes of pneumonia, elevation of C Reactive Protein, white cell count changes, positive blood culture.

3.8 Symptomatic:

3.8.1 Meconium aspiration syndrome (MAS)/ Persistent foetal circulation (PFC)

3.8.2 Air leaks (interstitial air, pneumothorax)

3.8.3 Intraventricular haemorrhage (IVH) - using Papile's grading system (18)

3.8.4 Necrotizing enterocolitis (NEC)

3.8.5 Acute tubular necrosis (ATN) (15)

3.8.6 Congestive cardiac failure / Tricuspid incompetence (CCF/TI) (15)

4. *ASSESSMENT*

The presence of developmental problems was assessed using a scoring system developed by Goodman (19), and the Early Language Milestones (ELM) Scales (20).

5. *OUTCOME*

Outcome at follow-up was defined as one of the following:

5.1 Normal

5.2 A speech / hearing problem only

5.3 A neurological deficit

5.4 A neurological deficit and seizures

5.5 A neurological deficit and speech / hearing / visual problems / ±seizures

6. *STATISTICS*

Results were analysed using multiple regression analysis, frequency analysis, descriptive statistics and simple correlations.

The study was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand (Clearance No. 11/10/91).

RESULTS

109 infants admitted to the Johannesburg Hospital Neonatal Intensive Care Unit (NICU) over the four-year period fulfilled entry criteria for this study and comprised the study group. The characteristics of these patients are shown in **TABLE 1**.

TABLE 1

Patient Characteristics

No. of patients	109
Sex M:F (%)	70:30
Birth weight (grams) mean±SD	2740 ± 555
Gestational age (weeks) mean±SD	36,4 ± 2,9
SGA (%)	2
Inborn:outborn (%)	57:43
Mode of delivery *Caesarean section* (%)	63%
Apgar score - mean : 1 minute 5 minute	2 3,5
Duration of ventilation (days) n(%) <1 1-3 4-7 >7	23 (21%) 43 (39%) 21 (19%) 22 (20%)
Hyaline membrane disease n(%)	45 (41%)
Pneumonia n(%)	9 (8%)
Air leaks n(%)	26 (24%)
Seizures n(%)	13 (12%)
Intraventricular haemorrhage (all grades) - grades 3 or 4	22 (20%) 0 (0%)
Necrotising enterocolitis n(%)	3 (3%)
Meconium aspiration syndrome n(%)	7 (6%)
Acute tubular necrosis n(%)	6 (5,5%)
CCF/ TI n(%)	5 (5%)

SGA=small for gestational age

Figures 2 and 3 show the distribution of birth weight and gestational age.

Figure 2

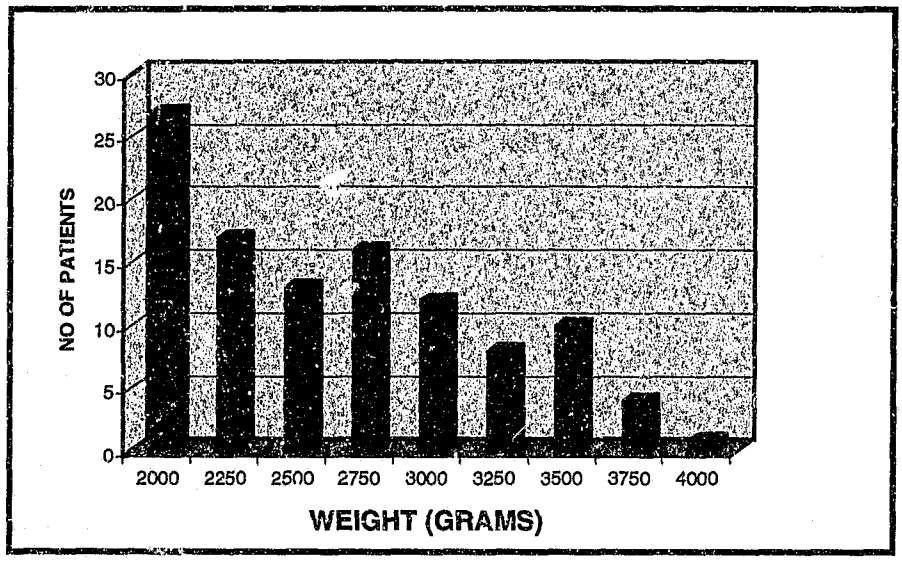


Figure 3

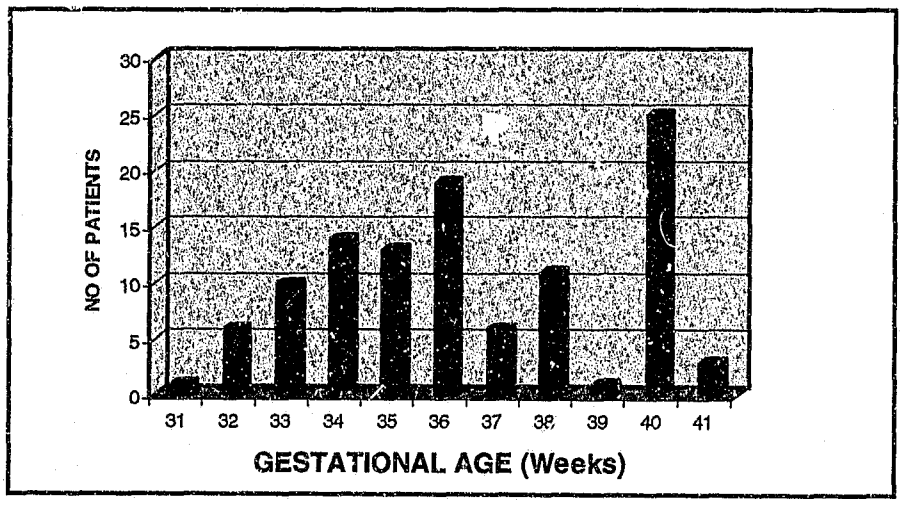
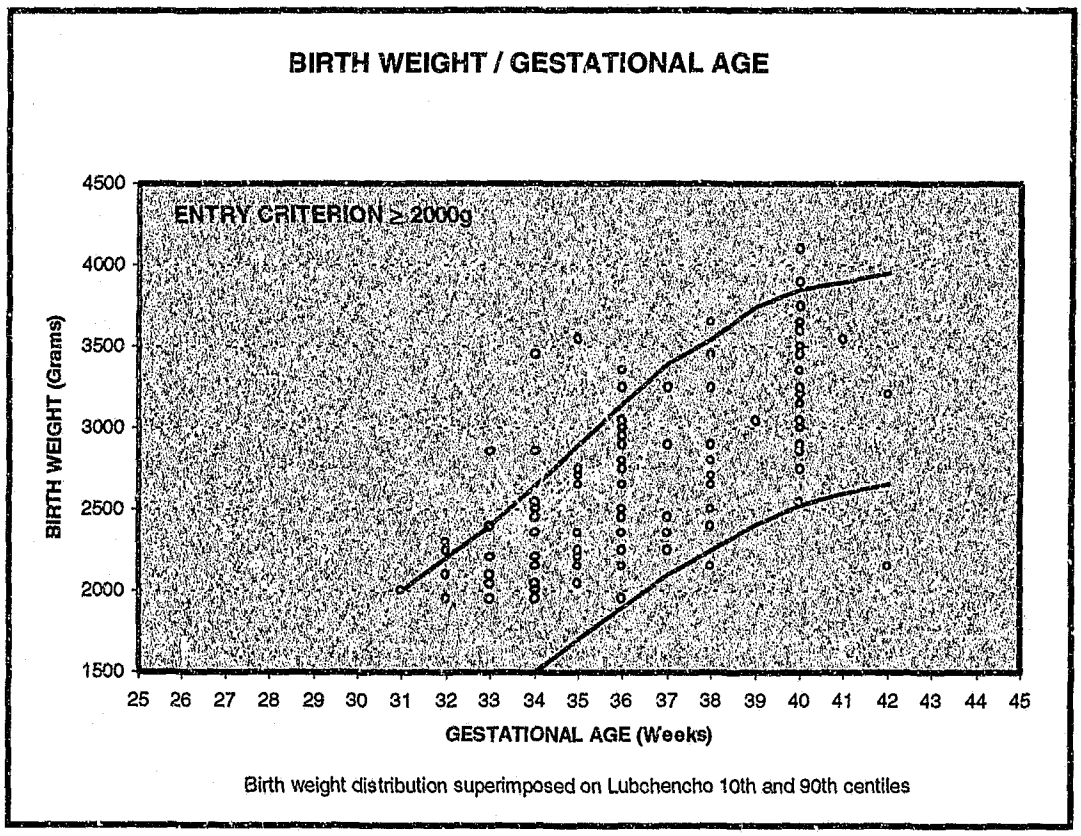


Figure 4 plots weight against gestational age and is superimposed on a Lubchenco growth chart (21). Some infants shown as large for gestational age are likely to have been misassessed in terms of gestational age rather than being truly macrosomic or hydropic. Such errors may be the result of hypotonicity (due to the asphyxia) interfering

with gestational age assessment which is partly based on tests involving muscle tone.

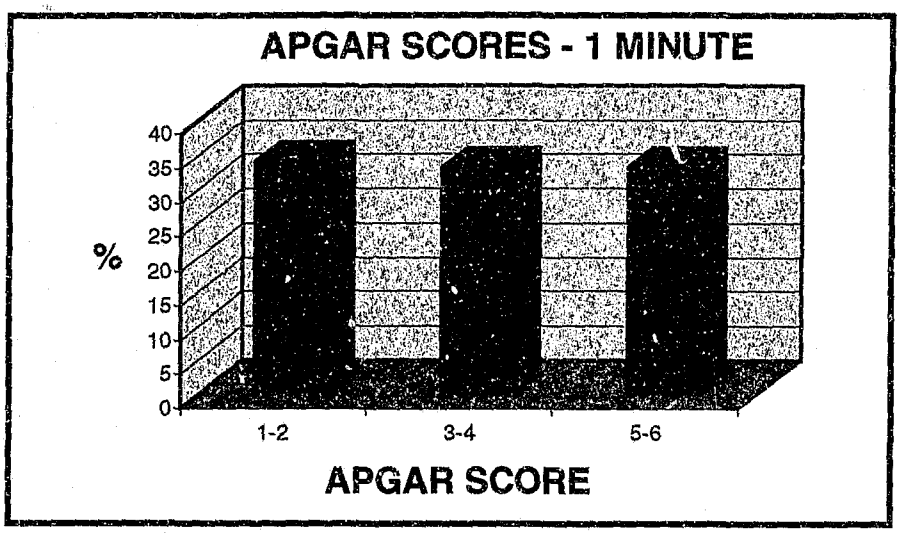
Figure 4



APGAR SCORES

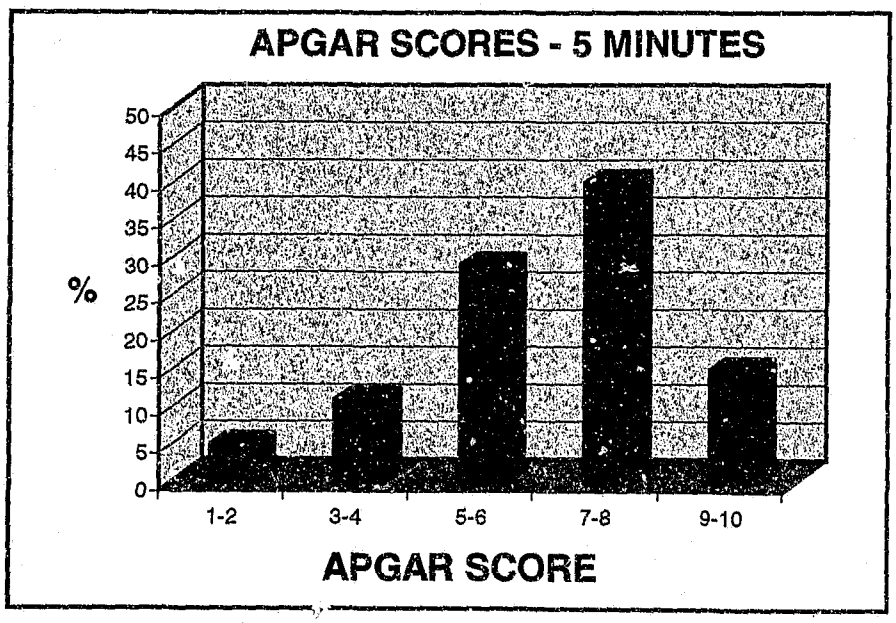
The 1-minute Apgar scores showed an almost equal distribution between the groups with Apgar scores of 1-2, 3-4 and 5-6. (Figure 5). Only a third of the patients had a 1-minute Apgar score of more than 4.

Figure 5: 1 Minute Apgar Score



Forty-five percent of the patients had a 5-minute Apgar score of 6 or less. (Figure 6)

Figure 6: 5 Minute Apgar Score



Forty-four (40%) were found to be normal at follow-up.

Forty-three (39.5%) patients failed to attend follow-up clinic.

Six (5.5%) of the study neonates were found to have a neurological deficit. This included cerebral palsy, seizures and speech and/or hearing problems.

Sixteen patients died (15%). Their characteristics are shown in Table 2.

TABLE 2

Deaths

Birth Wt (grams)	Apgar 1 & 5 min.	Mode of delivery	Age at death (days)	Other problems
3500	1 2	Caesarean	1	CCF
3860	1 3	NVD	1	ATN
2000	2 3	Caesarean	2	
2770	1 2	Caesarean	8	MAS, ATN, seizures
2880	3 4	Caesarean	2	PFC/MAS
2400	2 4	Caesarean	5	pneumonia
3100	1	NVD	8	IVH, NEC, ATN
3000	3 5	Caesarean	1	
3215	1 1	NVD	5	seizures
2025	1 2	Caesarean	2	IVH
2400	3 3	Caesarean	3	seizures
3000	2 4	Caesarean	1	PFC/MAS
2000	1 3	Caesarean	30	HMD
3925	1 3	Caesarean	5	seizures

NVD = normal vaginal delivery

A number of factors were studied in relation to deaths. (Table 3)

TABLE 3

Factors associated with Death in Newborns with Asphyxia

FACTOR	p
seizures	<0,05
CCF/TI/PFC/MAS	<0,01
Apgar - minute	NS
Apgar - 5 minute	NS
mode of delivery	NS
HMD	NS
pneumonia	NS
air leak	NS
IVH	NS
NEC	NS
ATN	NS
IUGR	NS
sex	NS
inborn/outborn	NS

NS = not significant

Multiple regression analysis revealed that CCF/TI and PFC/MAS correlated significantly with death. For the purposes of this study these cardio-respiratory consequences of asphyxia were then grouped together (CCF, TI, MAS, PFC) because their aetiologies are interdependent. As indicated above, using multiple regression analysis, and including the independent variables discussed under 'Patient Data' (page 11), it was shown that the aforementioned cardio-respiratory complications of asphyxia (CCF, TI, MAS, PFC) and seizures were significantly associated with death in asphyxiated

newborns.

Subsequent frequency analysis combining **all** manifestations (multi-organ) regarded as symptomatic of birth asphyxia revealed that the presence of such manifestations also correlated significantly with neonatal death, yielding an almost 2,5 times risk of death:

TABLE 4

Clinical Manifestations of Birth Asphyxia

	Deaths (n=16)	Survivors (n=93)
(CCF/TI; MAS/PFC; ATN; NEC; Seizures; IVH; Air leaks)	16 /16 (100%)	39/93 (42%)

Relative risk = 2,38; 95% confidence interval 1,88 - 3,03; ($p<0,001$)

Characteristics of the 6 patients with a poor neurological outcome are summarised in Table 5.

TABLE 5

Patients with Neurological Deficit

Birth Wt (grams)	Apgar 1 & 5 min	Mode of delivery	Neuro deficit	Other problems
2600	2 intub-ated	Caesarean	hearing	air leaks CCF/TI
3675	3 6	Caesarean	spastic hemiplegia, delayed speech	MAS/PFC, CCF/TI
3500	2 7	Caesarean	microcephaly, severe CP, no speech	seizures
3400	1 5	Caesarean	Severe spastic CP, no speech	seizures ATN
2360	5 9	Caesarean	hypotonic CP, seizures, delayed speech	IVH, seizures, air leaks
2040	2 7	Caesarean	no speech	IVH air leaks

CP=cerebral palsy

Regression analysis again showed that seizures and the previously defined cardio-respiratory complications of asphyxia were significantly associated with a poor neurological outcome. (Table 6)

TABLE 6

Factors associated with Poor Neurological Outcome in Survivors

FACTOR	p
seizures	<0,001
CCF/TI/PFC/MAS	<0,001
Apgar - 1 minute	NS
Apgar - 5 minute	NS
mode of delivery	NS
HMD	NS
pneumonia	NS
air leaks	NS
IVH	NS
NEC	NS
ATN	NS
IUGR	NS
sex	NS
inborn/outborn	NS

IVH/HIE=intraventricular haemorrhage/hypoxic ischaemic encephalopathy

When **all** patients with adverse outcome (death or neurological deficit) were compared with intact survivors, it was again found by frequency analysis (as described in Table 4) that the combination of symptoms of birth asphyxia correlated with adverse outcome (22/22 versus 53/87; p=0,001; relative risk=1,64; 95% confidence interval 1,39-1,94).

Furthermore, when mode of delivery was analysed in the two groups it emerged that Caesarean section was more frequent in those with adverse outcome (18/22 versus 52/87; p=0,056).

The following Table compares characteristics of the patients that were lost to follow-up with those that had a normal outcome. It shows that the groups are similar except for fewer Caesarean sections in the group that was lost to follow-up. This finding suggests that those lost to follow-up had fewer intrapartum/asphyxial problems and were consequently not delivered by emergency Caesarean section.

TABLE 7

Characteristics of lost patients

	Lost	Normal
No. of patients	43	44
Mean birth wt (grams)	2719±558	2740±540
Mean 1 min A.S.(range)	2,1 (1-3)	2,0 (1-3)
Mean 5 min A.S.(range)	3,5 (1-5)	3,5 (2-5)
Caesarean section n (%) *	21 (49)	31 (70)

*p=0,04

DISCUSSION

Perinatal asphyxia is one of the leading causes of perinatal deaths and is a well-recognized cause of neuromotor disability later in life among the survivors (22). Multiple system complications have been documented after clinically defined perinatal asphyxia. A major problem in the examination of these relationships has been the lack of a generally accepted measure of asphyxia (23)

An association has been shown between acidemia at delivery and newborn complications such as seizures, cardiac and respiratory complications, and renal damage. All studies support the contention that such complications occur when the acidemia is severe (i.e., umbilical artery pH<7,0) (24).

Virginia Apgar's dissatisfaction with the "unscientific observations" made on the condition of the newly born infant prompted her to develop the scoring system that bears her name (25). The Apgar score remains the only well-recognized method for clinical assessment of the newborn infant (26). However, despite its wide acceptance and use, the value of the Apgar score has repeatedly been questioned (27-29). Furthermore, Apgar scores are not solely a measure of intrapartum asphyxia but also reflect non-asphyxial stress at birth. Low birth weight and gestational age are among the factors which adversely affect Apgar score, even in the absence of birth asphyxia (30,31).

In 1986, the American Academy of Paediatrics suggested that the diagnosis of birth asphyxia should not be based solely on a low Apgar score (27). Marrin and Paes found

that it is a poor marker for asphyxia (28). It has also been found to be subjective, and assignment of the score is often retrospective giving it a poor predictive value for neurological disability (17,29). Despite its limitations, the Apgar score is still widely used in identifying the need for resuscitation in the delivery room and it has been reported in one study to be superior to the presence of cord blood acidosis (32). On the other hand, the routine use of the Apgar score in all deliveries makes it useful for retrospective identification of infants with possible asphyxia. This was the method used in the study presented here to primarily select infants for review.

Since low Apgar scores themselves are not synonymous with birth asphyxia, the score cannot be used to predict the outcome of birth asphyxia accurately (32). This was confirmed in the present study, where there was no correlation between the score and subsequent adverse outcome (death or neurological deficit).

Many different tests are available to help determine neurologic outcome after birth asphyxia in term infants. Most of those with a high positive predictive value require some element of special equipment and expertise, and many are not widely available. For example, magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) are particularly useful (33); however, the practicality of using these tests in the South African situation is limited.

In this study, records were reviewed and analysed for 109 infants with birth asphyxia defined as a 1 minute Apgar ≤6 and the need for ventilation. The most important finding was that poor neurological outcome and death were significantly associated with

the presence of neonatal seizures and cardio-respiratory manifestations of asphyxia as defined by MAS/PFC/TI/CCF (14). There was also a significant relationship between adverse outcome and the combination of asphyxial symptoms (i.e. cardiorespiratory, CNS, renal, and gastrointestinal).

Other studies have reported an association between encephalopathy and/or seizures following birth asphyxia and subsequent poor outcome. Nelson and Ellenberg reported a very high rate of cerebral palsy in children with low Apgar scores (5 minute Apgar score of≤5), neonatal signs of encephalopathy and neonatal seizures. Neonatal seizures without the other signs were not associated with an increased risk of cerebral palsy (34). Results of the present study are in keeping with these findings: all infants were ventilated, (therefore seizures were already 'complicated' i.e. they did not occur in isolation but in combination with a need for assisted ventilation as a result of respiratory depression and/or persistent significant hypoxaemia and hypercapnia), and poor outcome was found in infants with seizures and other manifestations of asphyxia.

According to the Dublin Collaborative Study, a seizure occurring within 48 hours of birth in an infant born at term is the most rigorously validated event reflecting intrapartum asphyxia, and such seizures are also most strongly predictive of either neonatal death or survival with handicap. Eighteen percent of infants with post-asphyxial seizures died and 25% were handicapped at one year of age (35). The observations in the present study are also consistent with the Dublin findings.

In terms of non-CNS manifestations of asphyxia, hypoxia results in hypercarbia and

acidosis which in turn leads to impaired vascular autoregulation and a decrease in myocardial function. In the heart, severe or prolonged asphyxia results in hypoxic cardiomyopathy which may present with hypotension, poor myocardial contractility, cardiomegaly, tricuspid incompetence and congestive cardiac failure (36). In the present study, the occurrence of one or more of these clinical signs was significantly associated with adverse outcome.

In an evaluation of a registry for infants with brain injury, Korst et al. found that of 47 term infants only 21% met all four American College of Obstetrics and Gynaecology criteria of acute intrapartum asphyxia i.e. cord pH≤7, persistent Apgar score≤3 at ≥5 minutes, and neonatal neurologic and multiorgan dysfunction. Among these infants with brain injury, 38% had pH ≤7, 55% had Apgar scores ≤3 at ≥5 minutes, 87% had seizures and 70% had multiorgan dysfunction (37). In the present study, seizures, ATN and cardiac and/or pulmonary vascular problems were also seen, therefore the findings concur with those of Korst et al.

Robertson and Finer found that early onset encephalopathy is the best single predictor of long-term outcome after acute perinatal asphyxia. Among infants with moderate encephalopathy, the risk of death was 5%, and the risk of severe handicap 20%; with severe encephalopathy, the risk of death was 27-60% and the risk of handicap 50-100% (38). In the present study, the combination of low Apgar score plus ventilation is reflective of moderate to severe encephalopathy, and the results are consistent with those of the latter authors.

In terms of the handicap rate in the present study, while the figure of 5,5% is extremely encouraging, it is difficult to accept it with certainty because of the high drop-out rate (40% of the study patients were lost to follow-up). On the other hand, both this study and that done previously by Wild (8) include indicators which suggest that the infants lost to follow-up were at lower risk for handicap than those which returned.

CONCLUSIONS

The accurate determination of prognosis for infants suspected of having suffered birth asphyxia is a common clinical problem; assessment of the neurological prognosis of an individual affects decisions concerning appropriate levels of care, both in the neonatal period and in later childhood (33). This is especially important in South Africa where there is a lack of high care neonatal units (39) and facilities for children with neurological handicap.

In this 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. Caesarean sections were performed more frequently in the patients with a poor outcome, which is consistent with the hypothesis that damage had already occurred at the time of detection of fetal compromise, and fetuses were most likely manifesting signs of an acute-on-chronic insult.

The practical implication of this study is that moderate to severe asphyxia (as defined by low Apgar score and need for assisted ventilation) is likely to be relatively innocuous in the absence of other clinical manifestations. However, the presence of such manifestations confers a significant risk of adverse outcome (death or neurological handicap).

A disturbing feature of this study is the loss of infants from follow-up. However, social circumstances of the population have changed since the time of the study such that

access to the hospital and transport are much easier in 2000 than they were in the early to mid 1990's. Only with complete data will it be possible to state confidently that the apparent positive trends in mortality and handicap rate are real.

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