

**THE CONTRIBUTION OF INTRAPARTUM
ASPHYXIA TO THE DEVELOPMENT OF
CEREBRAL PALSY IN FULL TERM INFANTS-
A SYSTEMATIC REVIEW**

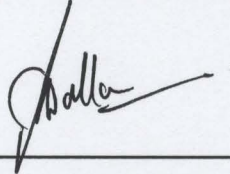
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**A research report submitted to the Faculty of Health Sciences, University of
the Witwatersrand, Johannesburg, in partial fulfillment of the requirements
for the degree of Master of Science in Medicine.**

Johannesburg 2012

DECLARATION

I, Mohammed S Nalla, declare that this research report is my own work. It is being submitted for the Degree of Master of Science in Medicine (Child Health – Neurodevelopment) at the University of Witwatersrand, Johannesburg. It has not been submitted for any degree or examination at this or any other university.



Mohammed. S. Nalla

On this _____12_____ day of _____ April _____ 2012.

DEDICATION

1. With gratitude to my darling wife, Yasmeen Nalla, for rearing our children, Layla and Zaeem, thereby allowing me the opportunity to complete my studies successfully with her unreserved support. Let the love bloom forever.
2. In loving memory of my late father, Ismail Nalla (1943 – 2008), who gave me the inspiration to persevere, but did not witness the completion of my degree.

ABSTRACT

Background

Brain injury that occurs during the intrapartum period remains one of the most commonly recognised causes of severe long-term neurologic deficits in infants and children, termed "Cerebral palsy" (CP). A much-debated question relates to the extent of contribution of asphyxia to CP since "birth" asphyxia was previously believed to be an important and obstetrically preventable cause of cerebral palsy. Recently, researchers have increasingly argued that most cases of cerebral palsy arise during foetal development or the neonatal period rather than during labour.

Objectives

Primary objective: To ascertain the contribution of intrapartum asphyxia to the development of CP in full term infants.

Secondary objectives:

- Determine the proportion of births with intrapartum asphyxia.
- Determine the proportion of infants with intrapartum asphyxia that die.
- Contrast the contribution of intrapartum asphyxia to CP in low-middle and highly resourced settings.

Search strategy

I searched the Cochrane Controlled Trials Register (Issue 4, 2007), MEDLINE (1966 to April 2010), and references lists of identified studies. Unpublished studies were sourced in the "Proceedings on Priorities of Perinatal Care in South Africa" from 1982 to 2006.

Selection criteria

For the purpose of this analysis, all observational (cohort and case-control) studies published, and unpublished studies that met the minimum criteria of

intrapartum asphyxia as outlined were included. The studies were limited to newborns at 37 or more weeks completed gestation who had evidence of intrapartum asphyxia and developed CP at subsequent follow up (i. e., up to 5 years of age).

Data collection and analysis

The primary researcher (MN) independently extracted data and assessed studies for the inclusion in this review. The studies were then ratified for inclusion by two independent supervisors. Forty five studies were found, 38 excluded immediately. Of the seven remaining studies a further three studies were considered to only partially meet the inclusion criteria and were thus excluded. A fourth study, Yudkin 1995, was in two parts and only part two was selected .This left four studies for review.

Main results

The four studies included in this review were conducted between 1994 and 2006. All four studies adequately attempted to describe the association between intrapartum asphyxia to CP. The proportion of CP ascribed to intrapartum asphyxia varied from 20% to 24% in three studies, whilst one study which only included dyskinetic CPs reported a 58% intrapartum asphyxia rate. This review found the type of CP most commonly attributed to intrapartum asphyxia was of the spastic and dyskinetic CP type. Furthermore, there was limited evidence in the 4 studies reviewed to adequately answer the secondary objectives of this review.

Reviewers' conclusions

In term and near term infants, the rate of CP attributable to intrapartum asphyxia is between 20% - 24% but the level of evidence to support this conclusion is weak.

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CONTENTS:

DECLARATION	ii
DEDICATION.....	iii
ABSTRACT.....	vi
ACKNOWLEDGEMENTS.....	vi
TABLE OF CONTENTS.....	1
LIST OF FIGURES.....	4
LIST OF TABLES.....	5
LIST OF APPENDICES.....	6

Table of Contents

1.0 Introduction	7
1.1 Epidemiology of CP	7
1.2 Epidemiology of perinatal asphyxia:	8
1.3 Changing perspectives	8
1.4 Pathophysiology of asphyxia	9
1.5 Relationship between perinatal asphyxia and cerebral palsy	10
1.6 Defining asphyxia	11
1.7 The "Bermuda Triangle"	13
1.8 Lack of clarity in defining conditions	16
1.9 Motivation for study	17
2. OBJECTIVES	18
Primary objective:	18
Secondary objectives:	18
DEFINITIONS	18
Term	18
Intrapartum asphyxia	18
Cerebral palsy	19
3. CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW	19
Types of studies	19
Confounders that had to be described in studies	19
Types of participants	20
4. SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES	20
MEDLINE Search	20
Cochrane Controlled Trials Registry Search	21
5. METHODS OF THE REVIEW	21
Publication selection	21
Assessment of the quality of studies	22
Data analysis	22
6. DESCRIPTION OF STUDIES	23
6.1 Excluded studies	23
6.2 Included studies	23

6.2.1 Length of study	23
6.2.2 Participants	23
6.2.3 Inclusion Criteria	24
6.2.4 Study size	24
6.2.5 Outcomes	24
7. METHODOLOGICAL QUALITY	24
8.0 RESULTS	25
8.1 Studies included and excluded	25
8.2 Characteristics of included studies	25
8.3 Detailed description of included studies	26
8.3.1 Rosenbloom 1994	26
8.3.2 Yudkin 1995	27
8.3.3 Hagberg 2005	28
8.3.4 Gurbuz 2006	29
8.4 Characteristics of excluded studies	30
8.5 Study outcomes	31
8.6 Geographical origin	32
8.7 Study periods	32
8.8 Number of participants	32
8.9 Study designs	32
8.10 Length of follow-up	32
8.11 Definition of Cerebral Palsy	33
8.12 Definition of intrapartum asphyxia	33
8.13 Outcomes relating to reviewed studies	33
8.13.1 Cerebral palsy type	34
8.13.2 Developmental delay and visual impairments	35
8.13.3 Seizures	35
8.13.4 Neonatal encephalopathy	35
8.14 Link between intrapartum asphyxia and CP	35
8.15 Neonatal mortality	37
8.16 Frequency of CP	38
8.17 Summary of the main findings:	39

9.0 DISCUSSION.....	40
9.1 Principal findings	40
9.2 The contribution of intrapartum asphyxia to CP	41
9.3 Secondary objectives	42
9.3.1 Neonatal mortality in infants with intrapartum asphyxia.....	43
9.3.2 Other outcomes.....	43
9.3.3 Types of CP.....	44
9.4 Limitations of this review	44
9.5 Future research.....	45
10. Conclusion	45
REFERENCES.....	46
References to studies included in this review.....	49
References to studies excluded in this review.....	50

LIST OF FIGURES

Figure 1	Venn diagram illustrating relationships between neonatal encephalopathy, CP, intrapartum asphyxia, non-CP neurodevelopmental disability and normality.....	14
Figure 2	Schematic diagram illustrating relationships between foetal status, intrapartum asphyxia, neonatal encephalopathy and eventual outcome.....	16
Figure 3	Proportional rate of intrapartum asphyxia to CP.....	36
Figure 4	Neonatal mortality rate.....	37
Figure 5	Frequency of CP.....	38

LIST OF TABLES

Table 1 – A summary of the 4 included studies.....	26
Table 2 – A summary of the 4 excluded studies.....	31
Table 3 – A summary of the CP types in children identified with evidence of perinatal asphyxia.....	34
Table 4 – Frequency of CP as reported in two studies.....	38

LIST OF APPENDICES

APPENDIX A: Screening tool for inclusion of studies.....	51
APPENDIX B: Data extraction form for CP attributed to intrapartum asphyxia.....	53
APPENDIX C: Characteristics of excluded studies.....	57
Ethical Clearance Form from the University of Witwatersrand.....	61

BACKGROUND

1.0 Introduction

Cerebral palsy (CP) is not a disease but is, rather, a category of disability including patients with one kind of problem: chronic non progressive disorders of movement or posture of early onset. The anatomic sites of involvement, degree of motor disability, associated dysfunctions, and cause are heterogeneous. The term "cerebral palsy" is comparable with the term "mental retardation," which describes persons with problems of intellectual function. Just as it is reasonable to ask, "What proportion of mental retardation is caused by Down syndrome?" so it is reasonable to ask, "What proportion of CP is caused by birth asphyxia?" (Nelson 1988).

1.1 Epidemiology of CP

Prevalence rates for cerebral palsy vary somewhat in different countries and regions, reflecting economic and nutritional factors and access to good obstetric care. Because of the absence of any "test" for cerebral palsy, the vagueness and elasticity of even the best definition, inaccurate ascertainment and lack of agreement between different experts in the inclusion of individual cases, precise figures are difficult to obtain. Further confusion results because many cases die in infancy and others may be so mild as to be unrecognised.

After an initial decline in childhood prevalence, the rate has increased slowly and steadily. This increase may be due to improved survival of very low birth weight infants (i.e. <1500g). However, a causal explanation for the increase in prevalence of CP has not been definitely established yet. Incidence figures should be based on the total population under study and not simply on survivors-if cerebral palsy is only recorded in those infants who live past the first birthday, for example, the figures will

imply a different contribution of obstetric and neonatal care to disability in the population from that derived from a consideration of all births.

1.2 Epidemiology of perinatal asphyxia

The incidence of perinatal asphyxia in term infants in industrialised countries varies between 2.9 and 9.0 per thousand live births (Haider 2006). The incidence of perinatal asphyxia in developing countries is, however, significantly higher ranging from 4.6 per 1000 in Cape Town, 6.7/1000 in Johannesburg (Saloojee and Cooper 1995) to 26 per 1000 in Nigeria (Haider 2006). In a recent study (1998) at Harare University Hospital in Zimbabwe, the incidence of perinatal asphyxia, defined as an Apgar score of five or less at 5 min, in singleton term babies was 15 per thousand live births (Wolf 1998). At Mpilo Central Hospital, a tertiary referral hospital in Bulawayo, the incidence was 19 per thousand live births in term babies (Wolf 1998). It has been estimated that perinatal asphyxia is responsible for 3 – 21% of the cases of cerebral palsy (Gurbuz 2006). The contribution of perinatal asphyxia to the incidence of cerebral palsy in developing countries is not known given the difficulties in accurately recognizing asphyxia and its timing and the lack of accurate epidemiological data.

1.3 Changing perspectives

For over a century, the etiology of CP has been the subject of considerable scientific speculation. In 1862, John Little, an orthopedic surgeon, suggested that cerebral palsy resulted from difficulties that arose during labour and delivery (Shields 1988). Much has changed in 100 years and a growing body of literature questions the truth of this belief because of the weakness of the association of intrapartum asphyxia with CP, the relative strength of the association of CP with indicators of adverse antenatal events, and the apparent lack of association of CP with poor obstetric care (Blair 1988). Sigmund Freud in 1897 was one of the first to offer the different perspective that adverse foetal events earlier in development cause both birth complications and CP (Rosenbloom 1994).

For a variety of reasons which include the fact that litigation in the USA, UK and Australia is having negative effects on both obstetric care and the profession – the

basis for this alternative view is now well established. Based on Western Australian epidemiological studies, Blair and Stanley (1988) suggested that intrapartum asphyxia was the cause of only 8 to 10 per cent of cases of CP. Researchers have increasingly argued that most cases of cerebral palsy arise during foetal development or the neonatal period rather than during labour. This is a complex issue, and this review will attempt to assess the contribution of intrapartum asphyxia to the development of cerebral palsy in full term infants.

1.4 Pathophysiology of asphyxia

It is generally accepted that during significant asphyxia there is simultaneous occurrence of hypoxia and hypercarbia, which leads to foetal respiratory and metabolic acidosis. The acidosis results from the retention of carbon dioxide and the accumulation of lactic acid from anaerobic metabolism of glucose when oxygen is not available. Since asphyxia is a disturbance from the normal, measured on a continuous scale, it can, in principle, occur in any degree. Because there is no direct measure of the asphyxial insult which initiates and maintains the subsequent biochemical process, markers of asphyxia must be secondary; a reflection of the foetal response to its disturbed conditions, rather than the disturbed conditions themselves. In practice, studies attempting to quantify the association between perinatal asphyxia and cerebral palsy have used various markers of assumed asphyxia, including a prolonged low Apgar score, and neonatal encephalopathy (often referred to as hypoxic-ischaemic encephalopathy) (Yudkin 1995).

The resultant brain injury due to the asphyxial process that occurs during the intrapartum period remains one of the most commonly recognised causes of severe long-term neurologic deficits in infants and children, which often is termed "cerebral palsy" (CP) (Stanley 2000).

It is widely accepted that permanent motor deficit can be caused by asphyxia but only if the asphyxia was severe and prolonged. Evidence of such "substantial" asphyxia will be manifest during labour, delivery, and the neonatal course. To attribute cerebral palsy to

intrapartum asphyxia alone, one must have both an absence of other demonstrable causes and the presence of a sequence of signs during labour, delivery, and the perinatal period.

As a better understanding of the pathogenesis of neurologic dysfunction of the neonate has developed, it has become increasingly clear that neonatal encephalopathy and cerebral palsy may frequently have origins in the antepartum period. Although it appears that the majority of neurologic injuries (asphyxial or nonasphyxial) predate labour, labour is, nonetheless, a time of risk for hypoxaemia and acidaemia and a time, therefore, during which increased foetal surveillance is warranted (Fahey 2005).

1.5 Relationship between perinatal asphyxia and cerebral palsy

Estimates of the fraction of cerebral palsy arising from asphyxia have been made in various ways. The simplest and most direct method is retrospective examination of the perinatal history of infants with cerebral palsy, to identify those cases that appear to be asphyxial in origin.

During the last two decades, researchers have critically examined the links between birth asphyxia and cerebral palsy from a clinical perspective. Freeman and Nelson (1988) epitomised those views and concluded that to reach a rational conclusion about whether a person with cerebral palsy, who was born at term, acquired his or her disability because of intrapartum asphyxia, a series of criteria need to be fulfilled. The answer to all of these questions must be affirmative before anything approaching a reasonable medical certainty of causal relationship can be supported.

1. Was there evidence of marked and prolonged intrapartum asphyxia?
2. Did the infant, as a newborn, exhibit signs of moderate or severe hypoxic-ischemic encephalopathy during the newborn period, with evidence also of asphyxial injury to other organ systems?
3. Is the child's neurologic condition one that intrapartum asphyxia could explain?
4. Has the workup been sufficient to rule out other conditions? (Freeman 1988).

The stronger and more clear-cut evidence is for an affirmative answer to all these questions, the more likely that intrapartum asphyxia was the cause of cerebral palsy. Even

when asphyxia was present, it must be acknowledged that pre-existing malformation or neurologic abnormality in the child may have contributed to the occurrence of the asphyxia. Once intrapartum asphyxia is properly determined to be the cause of a child's cerebral palsy, one can then assess whether or not the asphyxia was preventable and whether or not the patient was properly managed (Freeman 1988). Similarly, even in the presence of a diagnosis of intrauterine asphyxia, an affirmative to the above adverse neurologic outcome should not be attributed to intrapartum events unless the criteria outlined are met.

Not only is causation of neurologic injury difficult to establish, but identifying the timing of the injury is also complicated. Any estimate must be conjectural given the difficulties in accurately recognizing asphyxia, and its timing. Methodological problems make similar estimates in developing countries and in previous epochs even harder, but they are likely to be significantly greater. Intrapartum asphyxia is likely to contribute more as a significant cause of CP.

1.6 Defining asphyxia

In the last decade, two major task forces have provided guidance on differentiating cases of neonatal encephalopathy and cerebral palsy that may be due to intrapartum events from those that are due to events predating labour. Both task forces have reviewed and evaluated the research available and solicited opinions and written contributions from leading clinicians and scientists.

In 1999, the International Cerebral Palsy Task Force published its consensus statement. The following year, the American College of Obstetricians and Gynaecologists (ACOG) convened the Task Force on neonatal encephalopathy and cerebral palsy, and their consensus statement was published in 2003. Both task forces published criteria needed to diagnose cerebral palsy as secondary to an acute intrapartum event, with slight differences (MacLennan 1999). Furthermore, consensus has also been reached that intrapartum asphyxia of sufficient severity to cause later CP must produce evidence of a significant acute neonatal neurologic dysfunction (i.e. neonatal encephalopathy.) Thus neonatal encephalopathy is a "way station" through which intrapartum asphyxia passes to later yield

CP and is invariably present if intrapartum asphyxia is causal for this eventual outcome (Shevell 2004).

The clinical diagnosis of intrapartum asphyxia is based on several criteria, the two main ones being evidence of cardio-respiratory and neurological depression, defined as an Apgar score remaining less than 6 at 5 minutes after birth, and evidence of acute hypoxic compromise with acidemia, defined as an arterial blood pH of less than 7 or basic excess of -12mmol /litre (MacLennan 1999). In many settings, especially in resource poor countries, it may be impossible to assess foetal or neonatal acidemia. In the immediate postpartum period when resuscitation is being undertaken, it may not be possible to determine whether the neurological and cardio-respiratory depression is secondary to hypoxic-ischaemia, or to another condition such as foeto-maternal infection or metabolic disease. Consequently, resuscitation and early management will often be of suspected rather than confirmed intrapartum asphyxia.

Listed below are "criteria sufficient to define an acute intrapartum hypoxic event", advanced by both the American College of Obstetrician and Gynaecologists (ACOG) (Hankins 2003) and The International C.P. Task Force (MacLennan 1999). The table below shows the template of evidence required to suggest the occurrence of damaging intrapartum hypoxia sufficient to cause permanent neurological impairment. Taken together, criteria 4 to 8 help to time the hypoxic event to the intrapartum period (MacLennan 1999).

Criteria to define an acute intrapartum hypoxic event as a cause of chronic permanent brain injury.

Essential criteria

1. Evidence of a metabolic acidosis in intrapartum foetal, umbilical arterial cord, or very early neonatal blood samples (pH <7.00 and base deficit > 12 mmol/l)
2. Early onset of severe or moderate neonatal encephalopathy in infants of > 34 weeks's gestation
3. Cerebral palsy of the spastic quadriplegic or dyskinetic type

Criteria that together suggest an intrapartum timing but by themselves are non-specific

4. A sentinel (signal hypoxic event occurring immediately before or during labour)

5. A sudden, rapid, and sustained deterioration of the foetal heart rate pattern usually after the hypoxic sentinel event where the pattern was previously normal
6. Apgar scores of 0-6 for longer than 5 minutes
7. Early evidence of multisystem involvement
8. Early imaging evidence of acute cerebral abnormality

(MacLennan 1999)

All three of the essential criteria are necessary before an intrapartum hypoxic cause of cerebral palsy can begin to be considered. If any one of the essential criteria is not met, it strongly suggests that intrapartum hypoxia was not the cause of the cerebral palsy. When all three essential criteria are met it is then necessary to determine whether the hypoxia was acute or chronic. If evidence for some of criteria 4 to 8 is missing or contradictory, the timing of the onset of the neuropathology becomes increasingly in doubt. Individually, these latter criteria are only weakly associated with an acute intrapartum damaging hypoxic event because, with the exception of criterion 4 (a sentinel hypoxic event), they may be caused by other factors such as infection. Logically, most of the final five criteria would have to be present for the balance of probabilities to suggest an acute timing to the hypoxic event. Contrary evidence, rather than missing evidence – for example, a normal Apgar score at 5 minutes – would weigh against a serious acute event (MacLennan 1999).

1.7 The “Bermuda Triangle”

The terms “cerebral palsy”, “neonatal encephalopathy”, and “intrapartum asphyxia” are all concepts integral to an understanding of neonatal neurology. Shevell has termed this type of morbidity as the “Bermuda triangle” (Shevell 2004). It is recognised that intrapartum asphyxia is but one cause of neonatal encephalopathy. Indeed, there is strong evidence to suggest that, as for CP, it is only an infrequent cause (Shevell 2004). However, neonatal encephalopathy at a moderate or severe level is a necessary antecedent to later CP if intrapartum asphyxia is causally responsible for the CP. Epidemiologic prevalence data highlight the scope of the problem. CP occurs in 1.5 to 2.5/1000 live births, neonatal encephalopathy, in 1.8 to 7.7/1000 live births, and intrapartum asphyxia, in 1.5 to 3.0/1000 live births. The

following figures, 1 and 2 illustrates the interrelationships between them (Shevell 2004).

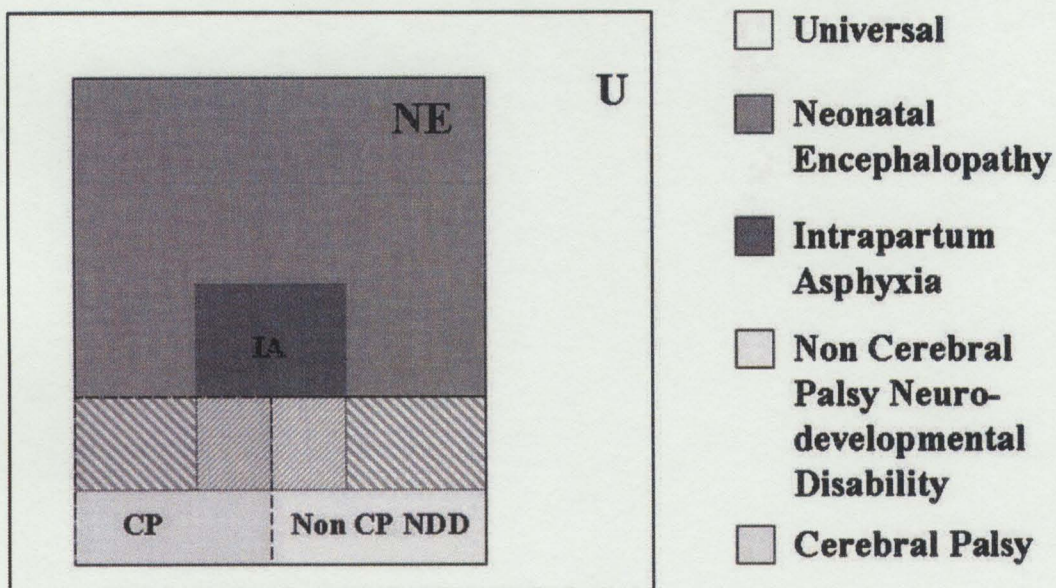


Figure 1.

Venn diagram illustrating relationships between neonatal encephalopathy, cerebral palsy, intrapartum asphyxia, non-cerebral palsy neurodevelopmental disability and normality (Shevell 2004).

Added explanation of figure 1:

The diagonal lines above the "CP column" represents CP with neonatal encephalopathy but no intrapartum asphyxia.

The diagonal lines above the "Non CP NDD" represents Non CP NDD with no intrapartum asphyxia but neonatal encephalopathy.

Relationships between CP, neonatal encephalopathy and intrapartum asphyxia

Based on our present knowledge and understanding, it is possible to elaborate a number of statements regarding the interrelationships between CP, neonatal encephalopathy, and intrapartum asphyxia within the context of children encountered in practice (i.e. those with and without neurodevelopmental disability). Their relationships are shown schematically in Figure 1 and are listed below:

- Some children with neonatal encephalopathy will have intrapartum asphyxia.
- All children with CP secondary to intrapartum asphyxia will have a degree of neonatal encephalopathy.
- Some children with intrapartum asphyxia will develop later CP.
- Some children with neonatal encephalopathy and no intrapartum asphyxia will develop later CP.
- Some children with later CP will have had previous neonatal encephalopathy and no intrapartum asphyxia.
- Most children with later CP will not have previous intrapartum asphyxia.
- Most children with later CP will not have previous neonatal encephalopathy.
- All children with CP will have a neurodevelopmental disability.
- Some children with a later non-CP neurodevelopmental disability will have had previous intrapartum asphyxia.
- Some children with a later non-CP neurodevelopmental disability will have had previous neonatal encephalopathy but no intrapartum asphyxia.
- Most children with a later non-CP neurodevelopmental disability will not have had previous neonatal encephalopathy.
- Some normal children will have had previous intrapartum asphyxia.
- Some normal children will have had previous neonatal encephalopathy but no intrapartum asphyxia.

The relationships between causes, neonatal presentation, and outcome are also shown schematically in Figure 2. The figure highlights the fact that foetal predisposing conditions may or may not exist as an antecedent of possible intrapartum asphyxia. A multitude of possible causes other than intrapartum

asphyxia exists to explain neonatal encephalopathy. There also exists a multitude of possible outcomes subsequent to neonatal encephalopathy, ranging from normality to CP to a non-CP neurodevelopmental disability. Causes other than those operating through intrapartum asphyxia and / or neonatal encephalopathy may also result in CP and non-CP neurodevelopmental disability. Thus neonatal encephalopathy is a “way station” through which intrapartum asphyxia passes to yield later CP and is invariably present if intrapartum asphyxia is causal for this eventual outcome (Shevell 2004).

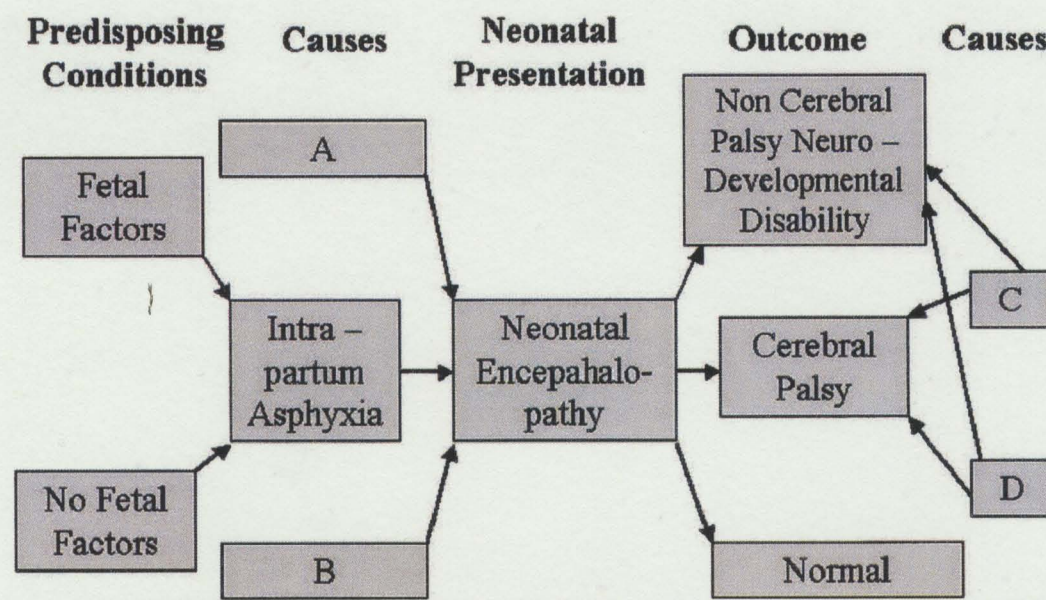


Figure 2. Schematic diagram illustrating relationships between foetal status, intrapartum asphyxia, neonatal encephalopathy and eventual outcome (Shevell 2004).

1.8 Lack of clarity in defining conditions

A particular problem of interpreting the results of research in this field is the lack of consistent definition of events and conditions such as “asphyxia”, “intrapartum” and

“neurological disability.” Investigating the role of intrapartum asphyxia in causing neurological sequelae has proved difficult and has been hampered by the:

- Poor measures of intrapartum asphyxia and a lack of understanding of the degree of asphyxia which is needed to cause either transient neurological dysfunction or long-term neurological sequelae.
- The relative rarity and, often, the unexpectedness of intrapartum asphyxia which makes prospective data hard to obtain and force a need to rely on retrospectively collected data.
- Poor definition of the severity and acuteness of brain injury in the perinatal period.
- Length of the time it takes to reach a diagnosis of cerebral palsy.
- Difficulty in obtaining well defined population based outcome data (Frances 2000).

1.9 Motivation for study

Perinatal asphyxia continues to be a focus of research for clinicians interested in the prevention of brain damage. Intrapartum factors producing asphyxia were traditionally assumed to be the principal cause of CP. However, this assumption was challenged during the 1980's and 1990's and today it is suggested that 70% - 80% of cases of CP are due to prenatal factors and that perinatal asphyxia plays a relatively minor role.

Having a CP child for any parent is devastating, and questions regarding the unfortunate outcome and its relationship to the birth process will always be asked. Events occurring at the time of birth also are the subject of frequent legal activity, with health professionals being asked to defend the adequacy of their care. Hence, it is vitally important for clinicians to know the role played by either intrapartum asphyxial events or any other aetiological factors in the development of CP.

CP is not a unitary disease, and its complexity renders difficult efforts to prevent and minimize this disability. For most children with CP, a careful search may reveal a possible cause. However, much work needs to be done in elucidating the primary cause(s) of this condition.

Previous studies have reported widely different rates of CP attributable to intrapartum asphyxia. Trying to establish a more precise rate is what prompted and motivated me to undertake this review. This review will attempt to delineate the extent of the link between asphyxia and CP and examine the evidence that perinatal asphyxia causes or is at least associated with CP in full term infants.

2. OBJECTIVES

Primary objective:

To estimate the contribution of intrapartum asphyxia to the development of cerebral palsy in full term infants.

Secondary objectives:

- Determine the proportion of births with intrapartum asphyxia.
- Determine the proportion of infants with intrapartum asphyxia that die in the neonatal period.
- Contrast the contribution of intrapartum asphyxia to cerebral palsy in low-middle and highly resourced settings.

DEFINITIONS

Term

A child born at between 37 - 40 weeks completed gestation.

Intrapartum asphyxia

Is defined by the ACOG criteria (Hankins 2003) or at least 2 of the following criteria:

- A severe disturbance of oxygen supply to the foetus, which is first recognised during the first or second stage of labour.
- Infants with a pH <7.0 or a metabolic acidosis in the umbilical arterial cord

blood sample or a blood sample soon after birth.

- A low Apgar, i. e., ≤ 3 at 1 minute and < 7 at 5 minutes or later.
- Multisystem involvement and/or the development of neonatal encephalopathy (grades moderate or severe as defined by Sarnat and Sarnat -1976) (Rosenbloom 1994).

Cerebral palsy

Cerebral palsy describes a group of disorders of the development of movement and posture causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing foetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception, and / or behaviour, and / or by seizure disorder (Bax 2005).

3. CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All observational (cohort and case-control) studies that met the minimum criteria of intrapartum asphyxia were included.

Confounders that had to be described in studies

The following confounders had to be described and excluded as possible contributors to cerebral palsy for inclusion in the review:

- placental abruption
- transplacental anaesthetic or narcotic administration
- congenital cardiac or pulmonary abnormalities
- maternal opiates in the four hours preceding birth
- congenital sepsis
- twin / multiple births

Types of participants

Term newborns (37 or more weeks completed gestation) that had evidence of intrapartum asphyxia and developed cerebral palsy at subsequent follow up, and which was still present at, at least, one year of life.

4. SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

Search strategies were devised and run on the following electronic databases to identify studies relevant to this review report.

The following databases were searched:

1. The MEDLINE database from 1966 to 2010.
2. The Cochrane Controlled Trials Register (CENTRAL), the Cochrane Library Issue 4 (1990).
3. Further references from published papers were scanned for relevant papers.

A search was made for studies related to the topic of "intrapartum asphyxia and cerebral palsy." The specific search strategy for MEDLINE and the Cochrane Controlled Trails Registry as given below.

MEDLINE Search

Dates: 1966 – Dec 2010

Strategy - MESH

#1 Asphyxia-Neonatorum / all subheadings

#2 Asphyxia

#3 Cerebral palsy / etiology

#4 Apgar score

#5 labor,obstetric

#6 Birth asphyxia

#7 Intrapartum asphyxia

Cochrane Controlled Trials Registry Search

Strategy (Update Software)

#1 ASPHYXIA-NEONATORUM*: ME

#2 Intrapartum asphyxia

#3 Cerebral palsy

Reports of trials in all languages were considered. References and "related articles" of the identified studies were checked.

A further search for unpublished data was sourced in "Priorities in Perinatal Care Conferences," from 1982 to 2006. A list of 17 potentially relevant papers were extracted but the data did not meet the criteria for intrapartum asphyxia and outcomes, (i.e. CP types) as outlined for this review.

5. METHODS OF THE REVIEW

Publication selection

The primary researchers (MN) assessed the titles and abstracts of possibly eligible reports detected using the search strategies described. All relevant or potentially relevant studies were identified, and full reports of these obtained and evaluated. Studies that fulfilled the inclusion criteria in terms of design (observational studies) were evaluated for descriptive characteristics and methodological quality. (Appendix A) The searches identified 45 papers of potential relevance to the review. These 45

papers were initially selected by one reviewer (MN) according to relevance by reviewing the title and abstract. The selected studies were then analysed independently by two reviewers (KN and HS) using predetermined inclusion criteria. (Appendix A) Any disagreements regarding selection were resolved through discussion involving all three reviewers.

Assessment of the quality of studies

The study characteristics, and the study outcome measures were abstracted onto a screening tool for inclusion of study (Appendix A) and a pre-designed data extraction form (Appendix B). The following data was extracted:

- 1) Author, year of study, country in which study was done and language.
- 2) Methods: study design, inclusion and exclusion criteria.
- 3) Population: recruitment, sample size, age, and follow up period.
- 4) Outcome: reported outcomes and key results.
- 5) CP: type of CP, proportion of CP due to intrapartum asphyxia, mortality rates and frequency.
- 6) Study participants: number of term infants.
- 7) Confounding factors.

Data analysis

Data entry and analysis were performed by one reviewer (MN) and checked by an independent assessor (KN). For each included study, clinically important information was systematically extracted. (Appendix A)

6. DESCRIPTION OF STUDIES

6.1 Excluded studies

Thirty eight studies did not meet the review inclusion criteria as outlined and were excluded. The majority of these excluded studies were descriptive or discussion papers, or perinatal mortality surveys or antenatal risks factors that did not address the relevance to this review. Seven studies were potentially relevant studies and entered into a screening tool for inclusion of studies (Appendix A). Four studies were excluded (one a bi-directional study –Yudkin 1995) and reasons for exclusion are stipulated in *Results – Characteristics of excluded studies*.

Hence, these four studies (Blair 1988, Thornberg 1995, Yudkin 1995-part 1, Korst 1999) were excluded and were not suitable for inclusion. In total 41 studies were excluded.

6.2 Included studies

Four studies were identified for this review .The details are described in the table of included studies. (Table 1)

6.2.1 Length of study

Two studies provided a long-term follow-up from 1 to five years.

A further two studies provided longer follow-ups i.e. to age 10 and 17 years.

6.2.2 Participants

All the studies included participants that were newborns at 37 weeks completed gestation who had evidence of intrapartum asphyxia and developed cerebral palsy at subsequent follow up. The diagnosis of intrapartum asphyxia and CP was made according to the criteria previously outlined.

6.2.3 Inclusion Criteria

All observational (cohort and case-control) studies with participants that met the minimum criteria of intrapartum asphyxia were included.

Studies required participants to have intrapartum asphyxia and to develop CP as an outcome. All four studies satisfied the inclusion criteria and were included in the analysis. (See Appendix A and B)

6.2.4 Study size

Yudkin 1995 was by far the largest study (166 participants) whilst Rosenbloom 1994, Hagberg 2005 and Gurbuz 2006 included 17, 132 and 101 participants respectively.

6.2.5 Outcomes

All the studies provide data on long term follow-up of at least one year.

Chosen outcomes varied between the studies. The main outcomes in all four studies were CP of the spastic or dyskinetic types. One study reported further outcomes of mixed, tetraplegic, hemiplegic, hypotonic, ataxic, athetoid and diplegic CP. Other reported outcomes in the analysis were neonatal encephalopathy, developmental delay, visual impairment, seizures and death.

7. METHODOLOGICAL QUALITY

This review did not attract a methodological quality analysis since the included studies were not randomised control trials. All the studies included in this review were either cohort or case control studies.

8.0 RESULTS

8.1 Studies included and excluded

Forty five potential studies were sourced for inclusion in this review; 38 studies were excluded due to them not meeting the review inclusion criteria. The reasons for exclusion of the 38 studies are outlined in the table, "Characteristics of excluded studies" (Appendix C). Of the seven remaining studies a further three studies were considered to only partially meet the inclusion criteria and were thus excluded. A fourth study, Yudkin 1995 was in two parts and only part two was selected Yudkin 1995 – part 1, were later excluded for reasons stipulated below. This left four studies for review.

8.2 Characteristics of included studies

Four studies were found to be relevant and were included in this review (the study by Yudkin 1995 – part two was included). For the purposes of this review stringent criteria were applied in defining intrapartum asphyxia, CP types and term infants. The four studies that satisfactorily met the inclusion criteria are summarised in Table 1.

Table 1: Summary of the four included studies.

Author	Publication year	Data collection period	Country	Study design	Number of CP cases	Evidence of perinatal asphyxia (number)	CP attributable to intrapartum asphyxia (%)
Rosenbloom	1994	1967-1984	UK	Cohort	17	10	58
Yudkin	1995	1984-1985	UK	Cohort	15	3	20
Hagberg	2005	1991-1994	Sweden	Cohort	132	32	24.2
Gurbuz	2006	1990-2000	Turkey	Case-control	101	21	20.8

8.3 Detailed description of included studies

8.3.1 Rosenbloom 1994

Rosenbloom's 1994 cohort study collated data for the period 1967 – 1984 from the Alder Hey Children's Hospital in Liverpool, UK. This study examined the connections between perinatal asphyxia and dyskinetic CP from data collected in the Merseyside region of the UK. There were 1056 children with CP, of whom 115 had the dyskinetic or dystonic variety. Children included in this study had clinical evidence of dyskinetic CP, preservation of cognitive abilities, gestation of > 37 weeks and birthweight >10th centile for gestational age. Infants who presented with other types of CP were excluded from this study.

Of the 115 children with dyskinetic CP, 17 were born after 37 weeks gestation and were included in the study. These children were followed up for a period of 17 years. Ten of them were reported to have had evidence of foetal distress during labour, perinatal asphyxia and hypoxic ischaemic encephalopathy (HIE). The ten affected children were analysed for foetal distress very late in labour and shortly before delivery. The degree of perinatal asphyxia was estimated using the one-minute Apgar score for nine infants (Apgar score of 2 or less) and cord pH for the tenth. All the children showed a degree of depression or acidosis at birth. The degree of encephalopathy sustained by the infants was graded using the criteria of Sarnat and

Sarnat. Perinatal asphyxia was present in 10/17 term singleton infants, an estimated 58% of full term infants. Rosenbloom's study did not determine the proportion of infants with intrapartum asphyxia that died in the neonatal period.

8.3.2 Yudkin 1995

The cohort study by Yudkin 1995 collated data for the period January 1984 to September 1985 in infants born to residents of Oxfordshire during this period. This bi-directional study investigated two parts. In the first part of the investigation, infants that exhibited specified groups of hypoxic signs (severe acidemia measured in umbilical arterial blood, persistent low Apgar score, moderate or severe encephalopathy, and evidence of multi-organ system dysfunction.), were identified and followed to the age of 5 years, when their neurodevelopmental outcome (including the occurrence of cerebral palsy) was assessed. In the second part of the investigation the contribution of perinatal asphyxia to the overall rate of CP in the population was estimated by retrospective examination of the perinatal records of children with CP. The same cluster of hypoxic signs was used to identify infants possibly damaged by birth asphyxia. The results of the two approaches were then compared.

For the purposes of this review, only "part two" was relevant. Term singleton infants that exhibited a critical cluster of hypoxic signs were included in this study. There were 173 such infants among 8863 singleton deliveries at the hospital. Seven of these infants died in the neonatal period with congenital anomalies and the remaining 166 formed the study cohort. CP cases born outside the Oxfordshire region, infants of less than 37 weeks gestation and who had known antenatal problems were thus excluded from the study.

The degree of perinatal asphyxia in this study was estimated by using the four "must be" criteria for intrapartum asphyxia as outlined in this review and that of the American College of Obstetricians and Gynaecologists. Encephalopathy was classified as moderate and severe encephalopathy only. Moderate encephalopathy was characterized by lethargy for at least 12 hours after birth, hypotonia, impaired primitive reflexes, and the occurrence of seizures. Severe encephalopathy involved

extreme hypotonia, with a need for mechanical ventilation, weak or absent primitive reflexes, and prolonged or repetitive seizures.

From the study cohort, 15 of the 30 children with CP were born at term of which three of the 15 cases of CP were attributed to perinatal asphyxia (low Apgar scores and umbilical arterial pH and moderate / severe encephalopathy). Children were followed up for a period of five years. Two of the deliveries were normal, one a caesarean section. Three infants developed seizures shortly after birth, one presented with severe encephalopathy and two with moderate encephalopathy. All three infants had spastic quadriparesis, with visual impairment and profound developmental delay, of which two also had epilepsy. Perinatal asphyxia therefore was associated with 3/15 cases of CP in term singletons, an estimated 20%. Yudkin's study was the only study from the four reviewed studies that calculated the proportion of infants that died in the neonatal period and found perinatal asphyxia was associated with 4/23 neonatal deaths (17.4%) in term singletons.

8.3.3 Hagberg 2005

Hagberg 2005 is a cohort study conducted in the western health care region of Sweden which collated data for the birth period 1991 – 1994. This aim of this study was to elucidate and time-relate the aetiology of CP in the majority of children born in Sweden. There were 113 724 live births recorded of which 107 260 were at > 36 weeks gestation. Hagberg 2005 defined term infants at >36 weeks gestation whereas the conventional definition is from 37 weeks gestation. Children with CP were included if they were born in Sweden and lived in the study area. All the children were at least 4 years of age when diagnosed with CP.

Intrapartum asphyxia was defined by a cluster of two signs, i. e., Apgar scores and HIE, whereas encephalopathy was considered in the presence of at least two of the following symptoms/signs: Apgar score of <5 at 1 or 5 minutes, resuscitation/ventilation, convulsions before day 3. This study included a cohort of 241 CP children, 132 children were born at term for whom consent for analysis was given. In 32 infants perinatal asphyxia was considered to have started intrapartum. Among these 32 infants, dyskinetic CP was the most frequent clinical subtype,

present in 19 (59%). The remaining 13 children had pure spastic CP subtypes.

In term births, perinatal asphyxia considered severe enough to cause CP was recorded and documented in 24.2%, with factors known to predispose to CP present in 30% of children. Although this study did not calculate the proportion of infants with intrapartum asphyxia that died in the neonatal period, a neonatal mortality rate of 3.3 per 1000 births was stipulated in this study.

8.3.4 Gurbuz 2006

The study by Gurbuz 2006 stood out because it originated from a less developed country - Turkey. This retrospective case-control study investigated the relationship between CP and perinatal and intrapartum risk factors and markers of perinatal asphyxia between 1990 - 2000. One hundred and one children with CP who were born at the Zeynep Kamil Women's and Children's Diseases Education and Research Hospital made up the study group, 308 children made up the control group. The control group was made up as follows: three controls for each case were selected by identifying the two babies born before and after the study case with the third control case selected randomly from the babies born within the same 8-hour period as the study case. Sixteen controls did not fulfill the study group selection criteria or had insufficient obstetrical records and were excluded from the study. Therefore 308 of the 324 control cases were included in the study.

The diagnosis of CP and inclusion criteria were as follows: children being at least 2 years of age, delivery at the Zeynep Kamil Hospital and a gestational age of 37 completed weeks or more. Children were followed up for a period of ten years. Infants with congenital malformations, multi-foetal pregnancy, any known cause in the postnatal period for CP development and preterm deliveries were excluded from the study.

Neonatal markers to diagnose perinatal asphyxia were Apgar scores and HIE. Encephalopathy was defined as depression at birth followed by evidence of neurological abnormalities such as lethargy, stupor, coma, and hyper-reflexia encountered during the first 48 hours of life, and was divided into three subgroups-

mild, moderate and severe.

HIE was detected in 14.9% of the CP group and 1% of the control group. This difference was statistically significant and neonatal HIE was found to cause a 17.7-fold increase in the risk of CP. A 5-minute Apgar score < 7 was detected in 21.8% of the CP group and 1.6% of the study group.

One or both markers of perinatal asphyxia, namely neonatal encephalopathy and low Apgar scores, were positive in 42.6% of the study group and in 6.49% of the control group. Possessing the markers of perinatal asphyxia increased the risk of development of CP 10-fold (OR 10.67, 95% CI 5.85–19.47). Twenty one of the 101 children with CP born at term showed evidence of perinatal asphyxia. The findings of this study suggest that perinatal asphyxia might be responsible for at least 20.8% of the cases with CP in this population. Gurbuz study did not determine the proportion of infants with intrapartum asphyxia that died in the neonatal period.

8.4 Characteristics of excluded studies

Four studies were excluded in this review for the following reasons:

Blair 1988, a retrospective study reported on CP cases diagnosed at age 5 years. The criteria used to define intrapartum asphyxia in this study met all four of the criteria as set out in this review. This study reported on spastic CP cases only which were closely and individually selected by birth weights. Blair's study was excluded due to the study not reporting specifically on full term infants who later developed CP.

Thornberg 1995 study reported on full term infants (gestational age > 37 weeks) and defined asphyxia by Apgar scores of < 7 at 5 minutes and hypoxic ischaemic encephalopathy. This study focused mainly on the clinical course and outcome of birth asphyxia/hypoxic ischaemic encephalopathic infants who later developed neurological sequelae and the study objectives were not relevant to this review.

Yudkin 1995 part 1, a bi-directional study used similar criteria to define asphyxia to that of this review and the criteria as set out by the American College of Obstetricians and Gynaecologist. This study reported on infants that exhibited hypoxic signs, and were followed to age 5 years, when their neurodevelopmental outcome was assessed. The first part of this study did not pertain to the objectives of this review and was excluded. The second part of the study, a retrospective review was included in this review.

Although Korst 1999 study met the four criteria for this review, i. e., (severe acidemia measured in umbilical arterial blood, persistent low Apgar score, moderate or severe encephalopathy, and evidence of multi-organ system dysfunction.), the objectives of this study did not pertain to the objectives of this review and this study did not address CP as the key outcome.

Table 2: Summary of the four excluded studies.

Author	Publication year	Data collection period	Country	Number of asphyxia cases	Number of CP cases	Intrapartum asphyxial cases that developed CP
Blair	1988	1975-1980	Australia	183	15	8.2%
Thornberg	1995	1985-1991	Sweden	227	10	4.4%
Yudkin	1995	1984-1985	UK	158	3	1.9%
Korst	1999	1990-1991	USA	292	25	8.6%

8.5 Study outcomes

All four included studies measured CP as the primary outcome following intrapartum asphyxia, but secondary outcomes varied between the studies. One of the included studies failed to report on CP prevalence rates and a further three studies did not report cohort mortality rates. There was some consistency in the types of secondary outcomes examined. This is detailed in the section on "Outcomes relating to reviewed studies."

8.6 Geographical origin

Three studies originated from well-resourced settings. Two studies were carried out in the United Kingdom (Rosenbloom 1994 and Yudkin 1995), one study in Sweden (Hagberg 2005), while the fourth study originated from a middle-income country (Turkey) (Gurbuz 2006).

8.7 Study periods

The studies included in this review spanned a 12 year period from 1994 until 2006. Two studies (Rosenbloom 1994, Yudkin 1995) were published in the 1990's:- Rosenbloom 1994 study was conducted during the period 1967 – 1984 whilst that of Yudkin 1995 spanned over a 20 month period (January 1984 – September 1985). A further two studies were published after 2000 (Hagberg 2005; Gurbuz 2006). Hagberg 2005 study was conducted over a four year period (1991 -1994) and that of Gurbuz 2006 was over a ten year period (1990 – 2000). From 2006 to December 2010, no further studies pertaining to intrapartum asphyxia and CP were published.

8.8 Number of participants.

The number of study participants in the four studies ranged between 17 and 166. The biggest study was that by Yudkin 1995 which included 166 participants, the smallest 17(Rosenbloom 1994). The other studies had sample sizes of 101 and 135. (Gurbuz 2006 and Hagberg 2005).

8.9 Study designs

All four of the studies were retrospective. (i. e., one study using a case control and three cohort study designs).

8.10 Length of follow-up

Two studies provided follow-up data for CP of one to five years, whilst one study each provided longer follow-ups of 10 and 17 years.

8.11 Definition of Cerebral Palsy

A clinical diagnosis of CP being met was reported by all four studies. However, three studies did not specifically define the criteria used to define CP in their published papers. The definition and the classification of the types of CP was explicitly offered in only one study (Hagberg 2005). This study clearly defined CP, and the CP subgroups were classified according to the Swedish and internationally accepted classification for CP syndromes. Gurbuz 2006 did not define CP or its subtypes but reported on the different CP subgroups in their study.

8.12 Definition of intrapartum asphyxia

One study (Yudkin 1995 part 2) used a definition that fulfilled all four criteria as outlined in this review and that of the American College of Obstetricians and Gynaecologists. Three studies met some, but not all four, of the review inclusion criteria for intrapartum asphyxia (Appendix A). These three studies met only two of the four criteria i. e., that of an Apgar score of <7 at 5 minutes and neonatal encephalopathy/HIE. The three studies were included in the review since they clinically diagnosed perinatal asphyxia although the criterion used in each of the studies partially satisfied the criteria set for this review and that of ACOG.

8.13 Outcomes relating to reviewed studies

Based on the studies reviewed, it is clear that the spastic quadriplegic and dyskinetic CP types were more strongly associated with evidence of perinatal asphyxia than the other subtypes of CP. Furthermore, spastic quadriparesis was more commonly found in term infants. Other outcomes, such as developmental delay, epilepsy and visual impairments, were reported by Yudkin 1995. One study, (Rosenbloom 1994) reported only on neonatal encephalopathy as an outcome, whilst seizures were reported in two studies. (Yudkin 1995, Hagberg 2005). Yudkin 1995 and Gurbuz 2006 also reported on neonatal encephalopathy but Yudkin 1995 was the only study to report on the neonatal death rates as a further outcome.

8.13.1 Cerebral palsy type

The spastic and dyskinetic CP types was the main outcomes in the four reviewed studies. Gurbuz 2006 also reported other types of cerebral palsy, i.e.; tetraplegic, hemiplegic, diplegic, mixed, ataxic and hypotonic types.

Yudkin 1995 reported only on children with spastic CP whilst Rosenbloom's 1994 study found 58% of children had dyskinetic CP. Rosenbloom did not report nor specify the CP types for the 42% of CP cases found in his study. A Swedish study, Hagberg 2005, reported 41% of spastic (including diplegia and hemiplegia) and a 59% dyskinetic CP type. Gurbuz 2006, reported 52.5% spastic CP and 7.9% dyskinetic CP. Gurbuz 2006 also identified mixed and ataxic CP in his study.

Table 3: A summary of the CP types in children identified with evidence of perinatal asphyxia.

Author, year	Country	Spastic CP (%)	Dyskinetic (%)	Mixed (%)	Other (%)	Comment
Rosenbloom 1994	UK	-----	<u>58</u>	-----	<u>42</u>	42% type of CP not reported
Yudkin 1995	UK	<u>100</u>	-----	-----	-----	Study only looked at spastic CP
Hagberg 2005	Sweden	<u>41</u>	<u>59</u>	-----	-----	Study found only spastic and dyskinetic CP
Gurbuz 2006	Turkey	<u>52.5</u>	<u>7.9</u>	<u>25.7</u>	<u>13.9</u>	Study found spastic, dyskinetic, mixed and other CP types

8.13.2 Developmental delay and visual impairments

Only Yudkin 1995 reported on these outcomes. Three of the six CP cases presented with either developmental delay, optic atrophy or cortical blindness.

8.13.3 Seizures

Two studies reported on seizures as an outcome. (Yudkin 1995 and Hagberg 2005) In Yudkin 1995, two of the six infants (33%) presented with seizures whilst in Hagberg 2005, 31 of the 32 infants (97%) presented with early neonatal seizures.

8.13.4 Neonatal encephalopathy

Rosenbloom 1994, Yudkin 1995 and Gurbuz 2005 reported on neonatal encephalopathy as an outcome in their studies. Yudkin 1995 reported all six cases having neonatal encephalopathy (3 moderate and 3 severe). Rosenbloom reported that 50% of the infants showed signs of moderate encephalopathy, whilst Gurbuz 2006 detected HIE in 14.9% of CP cases.

8.14 Link between intrapartum asphyxia and CP

All four studies adequately attempted to describe the association between intrapartum asphyxia and CP. Yudkin 1995 part 2, linked the association between intrapartum asphyxia to CP compared to the other three studies. All four (ACOG) criteria were used to measure asphyxiated infants in this study that later developed CP. Gurbuz 2006, Hagberg 2005 and Rosenbloom 1994 only accepted two major neonatal markers of perinatal asphyxia, namely low Apgar scores and neonatal encephalopathy for the diagnosis of perinatal asphyxia. Rosenbloom 1994 only examined the connections between intrapartum asphyxia and dyskinetic CP in his study. Three studies found that the proportion of CP ascribed to intrapartum asphyxia to be between 20% - 24%, whilst one study (Rosenbloom 1994) which only included dyskinetic CPs reported a 58% intrapartum asphyxia rate.

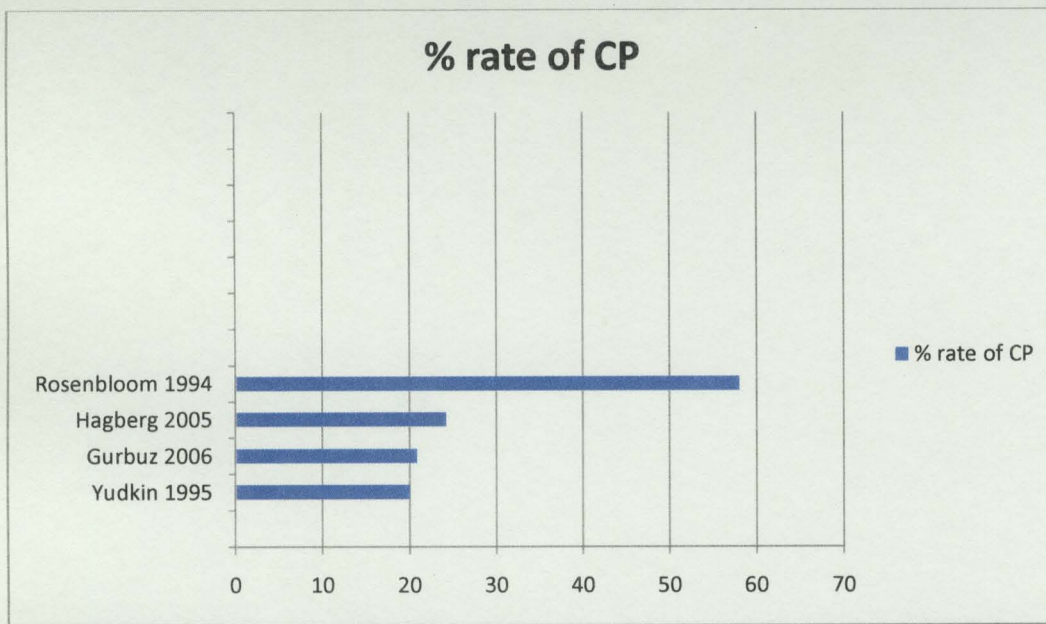


Figure 3: illustrates the Proportional rate of intrapartum asphyxia to CP reported in the 4 included studies.

8.15 Neonatal mortality

Only one study described neonatal mortality in infants with intrapartum asphyxia. Yudkin 1995 found a rate of 17.4% in her study. One other study (Hagberg 2005) merely reported on an average neonatal mortality rate of 3.3 per 1000 live births in Sweden. No other studies reported a neonatal death rate.

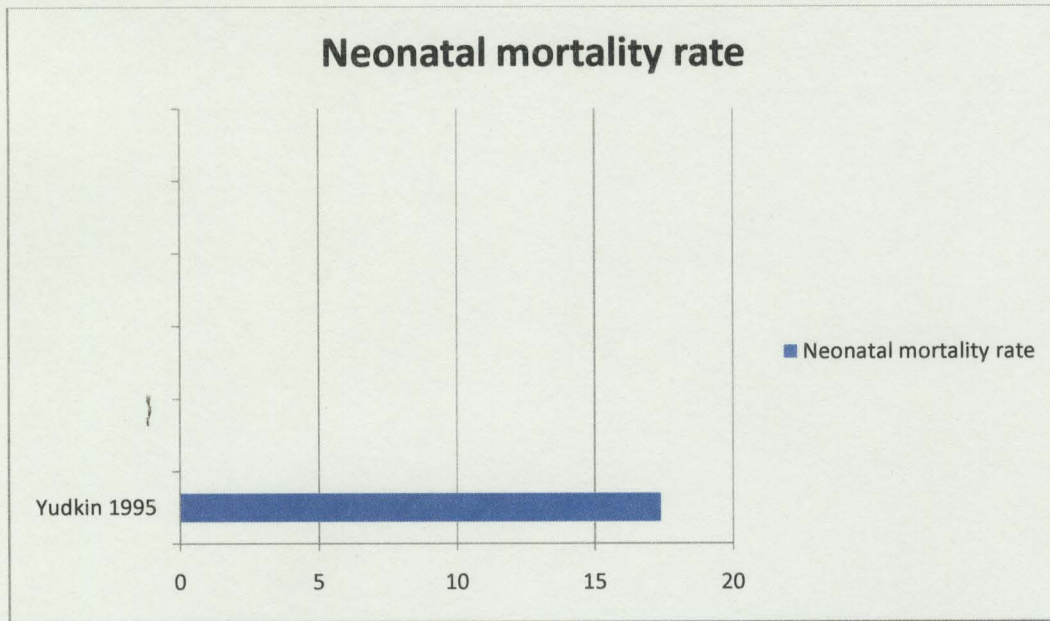


Figure 4: illustrates the neonatal mortality rate in the included studies, Yudkin 1995 study.

8.16 Frequency of CP

Two studies (Yudkin 1995, Hagberg) measured the frequency of CP from a cohort of CP infants. Based on the two review of studies, the frequency CP at term was measured to be 1.25 - 2.6 per 1000 singleton livebirths.

Table 4: The frequency of CP reported in two studies.

Author	Year of Publication	Data collection period	Country	No of births	No of CP	Frequency of term CP (per 1000 births)
Yudkin	1995	1984-1985	UK	11682	30	(30/11682) (2.6)
Hagberg	2005	1991-1994	Sweden	----	----	1.25 as reported

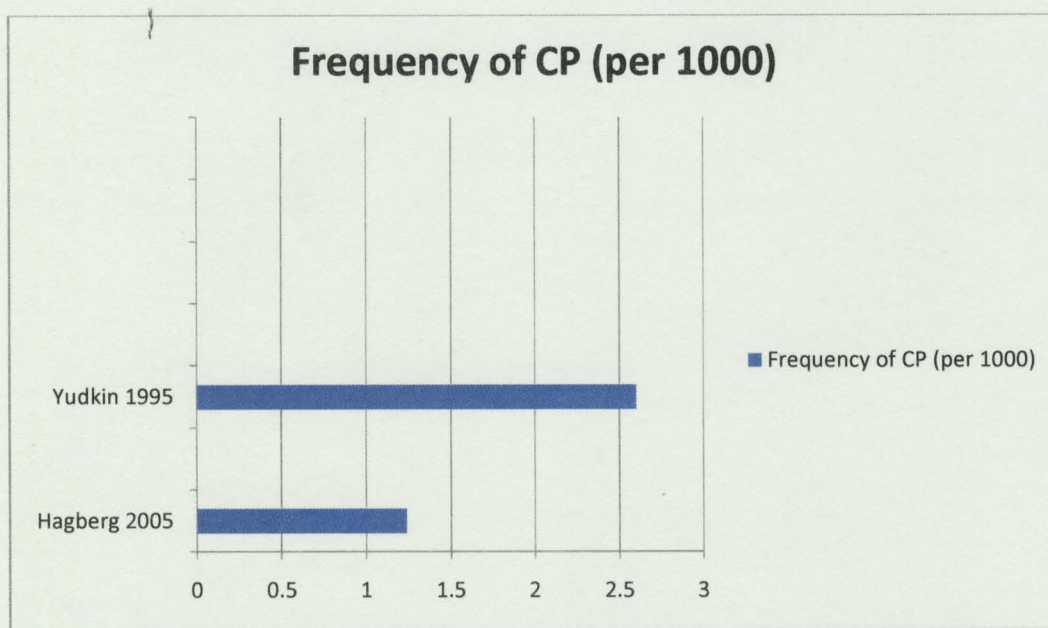


Figure 5: illustrates the frequency of CP as reported in two included studies.

8.17 Summary of the main findings:

- The proportion of CP ascribed to intrapartum asphyxia varied from 20% to 58% depending on the type of CP reviewed.
- The proportion of infants with intrapartum asphyxia who died was reported at 17.4% in the sole study where it was measured. (Yudkin 1995)
- The frequency of CP in term infants varied from 1.25 to 2.6 per 1000 singleton livebirths as reported in two studies.
- The type of CP most commonly attributed to intrapartum asphyxia was of the spastic and dyskinetic CP type.

9.0 DISCUSSION

9.1 Principal findings

This systemic review attempted to address a clear and focused question with explicit methodology. It offers the most up to date review of available studies, although none have been published in the last five years. It has identified major validity gaps, including variations in the criteria used in each study to diagnose perinatal asphyxia and the heterogenous nature of assessed outcomes of asphyxiated infants.

Even after careful selection of studies on the basis of predetermined criteria, comparing studies remained difficult. The main reason for this was the way test results were presented and studies did not provide sufficient data to draw reliable conclusions when addressing the secondary objectives of this review.

CP constitutes an important cause of life-long disability in the community. Finding causes of CP and establishing the timing of CP would be important for the prevention of this disease. It is therefore surprising that so few well-designed studies have addressed this important issue and that only four studies could be included in this review.

Several reasons could explain the scarcity of included high quality studies:

- Clinical research studies and randomised controlled trials are difficult to undertake in the setting of acute emergencies such as childbirth.
- Standardized and widely accepted diagnostic criteria for asphyxia and its consequences have only emerged in the last two decades.
- The study designs used had methodological limitations with a complete absence of a large prospective study.
- Sample sizes were small.
- Studies were heterogenous in terms of the type of CP reported and their secondary outcomes.

- Some studies did not differentiate between term and preterm infants resulting in their exclusion from this review.

9.2 The contribution of intrapartum asphyxia to CP

The primary objectives of this review was to ascertain the contribution of intrapartum asphyxia to the development of CP in full term infants. More than two decades ago, Blair and Stanley suggested that intrapartum asphyxia contributed to 10% of CP, and this became a consensus epidemiological and clinical viewpoint. However, this review challenges that dogma and draws attention to better designed studies suggesting a higher contribution of intrapartum asphyxia to the cause of CP of somewhere between 20 - 58%. Three studies in this review found similar rates of CP attributable to intrapartum asphyxia of between 20 - 24%, [Yudkin 1995 (20%), Gurbuz 2006 (21%) and Hagberg 2005 (24%)].

Previous and current studies leave huge gaps in our understanding of the contribution of intrapartum asphyxia to CP and researchers have frequently questioned the validity of reported rates of CP attributable to intrapartum asphyxia. Hence, can the rate found in the four reviewed studies be considered valid?

At the one extreme, Rosenbloom's 1994 study found a staggering 58% rate of CP ascribable to intrapartum asphyxia. However, caution is required in interpreting this statistic.

- In contrast to Yudkin 1995, Hagberg 2005 and Gurbuz 2006 studies, Rosenbloom 1994 study only identified and reported on dyskinetic CP. This study strongly emphasized that perinatal asphyxia is one of the most important cause of dyskinetic CP and the fact that Rosenbloom 1994 only looked at cases of dyskinetic CP cannot be used to as an indicator of the contribution of intrapartum asphyxia to CP in general.
- The study had a relatively small sample size.
- Severe asphyxia preceded by a sentinel event may produce mild to moderate HIE but has a high incidence of dyskinetic CP.

- None of the children in this retrospective study had undergone neuroimaging after a clinical diagnosis of CP was made in order to rule out any alternative pathology (degenerative or metabolic).

The study by Yudkin 1995 was the only study that conformed to the ACOG criteria and categorically addressed all four clinical markers for intrapartum asphyxia when diagnosing asphyxiated infants. Yudkin 1995 also found the criteria were a good starting point and it was found appropriate in that they clearly distinguished a small number of infants with a poorer prognosis. However, although the stringent ACOG criteria was successfully applied in Yudkin 1995 study, not all of the signs recommended by the ACOG were present in the six affected infants. The recommended cut-off points regarding Apgar scores and umbilical arterial pH were not always present in the affected infants.

On the otherhand, Hagberg 2005 and Gurbuz 2006 attempted to include the four ACOG criteria, but were unsuccessful and relied mainly on two major neonatal markers of intrapartum asphyxia, namely neonatal HIE and low Apgar scores for the diagnosis of perinatal asphyxia.

Three of the four studies were conducted in well-resourced settings. Of interest was that although Gurbuz 2006 originated from a middle income country, the rate of 20.8% of CP attributed to intrapartum asphyxia was similar to that described in better resourced settings (i.e., the studies by Yudkin 1995 and Hagberg 2005). The finding in Gurbuz 2006 study may be due to the study hospital's highly qualified maternity staff, and a setting that was adequately equipped to deal with high risk pregnancies that presented during or before labour because of acute or chronic foetal distress. Any extrapolation to other middle or low income settings would, therefore, be inappropriate.

9.3 Secondary objectives

The secondary objectives of this review were to evaluate the proportion of births with intrapartum asphyxia, the proportion of infants with intrapartum asphyxia that died in

the neonatal period and to contrast the contribution of intrapartum asphyxia to CP in low, middle and highly resourced settings. There is limited evidence in the four studies reviewed to adequately answer the secondary objectives. This was due to either limited and unavailable data in the four studies and the use of unsuitable study designs employed in the respective studies. Furthermore, the lack of comparable information between the studies made it difficult to assess neonatal mortality rates and to contrast the contribution of intrapartum asphyxia to CP in low, middle and highly resourced settings.

9.3.1 Neonatal mortality in infants with intrapartum asphyxia

Only one study in this review reported on neonatal mortality rates. (Yudkin1995) Hence, given the available data it was not possible to offer any conclusion on this.

9.3.2 Other outcomes

Outcomes other than CP and death need to be considered as a consequence of perinatal asphyxia. These include outcomes such as developmental delay, visual impairments, encephalopathy and seizures.

Seizures ranged from 33% (Yudkin 1995) to 97% (Hagberg's 2005). In Yudkin's 1995 study, 50% of asphyxiated CP infants developed visual impairments and developmental delay. There was heterogeneity in the type of longer term neurodevelopmental outcomes described for asphyxiated CP infants in the four reviewed studies and studies were deficient in the extent of detail offered on these outcomes.

Neonatal encephalopathy was described in three of the four studies and ranged from 14.9% (Gurbuz 2006) to 100% (Yudkin's 1995). This wide disparity may reflect the difference in the attention paid to the diagnosis or exclusion of HIE, but is more likely the result of different study inclusion criteria.

9.3.3 Types of CP

Based on the four studies reviewed, it is clear that the spastic and dyskinetic CP types were more strongly associated with evidence of perinatal asphyxia than the other subtypes of CP.

9.4 Limitations of this review

A key limitation of this review was that it was rather difficult to obtain and collate good quality studies to include in this review. This has limited the conclusions accordingly. I could not find adequate studies that conformed to the inclusion criteria as set out in this review. Furthermore, the heterogeneity found in most studies regarding the definition of intrapartum asphyxia and CP further hampered inclusion of studies and accurate analysis for this review. Forty five full - text studies were reviewed and found to be lacking in answering the secondary objectives of this review.

Another limitation was that I was unable to perform formal evaluations for publication bias due to the limited number of included studies. The potential for publication bias may be magnified since intrapartum asphyxia is not a PubMed index term, and there is no good agreement on the definition of intrapartum asphyxia. This makes searching for the relevant literature particularly challenging. Consideration should be given to creating a perinatal asphyxia index term to facilitate future searches for relevant evidence. I expect the evidence base about perinatal asphyxia and CP to change more rapidly in the near future than it has in the past.

Another limitation was that the initial screening of titles and abstracts was done only by myself, mainly because of the time and effort this required. However, the 45 articles subsequently selected were reviewed by two other colleagues (including one co-supervisor).

9.5 Future research

This review identified voluminous literature related to perinatal asphyxia and CP, but few quality studies. The available evidence was weak in answering the review's primary question. Researchers should be encouraged to build on existing trials to address this important issue. Large-scale prospective trials can be undertaken in the delivery room and future trials should stratify term and preterm infants and investigate the role and importance of the ACOG criteria when determining asphyxiated infants that later develop CP. They should also ensure that neonates are studied in the neonatal period examining for HIE which might be quite subtle. Further delineation of CP requires neurological skill to define types and degrees of disability. Furthermore, to ascertain the contribution of perinatal asphyxia to other chronic defects such as visual disturbance, intellectual impairments and seizures, these outcomes need to be included in prospective study designs.

10. Conclusion

A reasonable **conclusion**, based on the evidence of this review, is that for term infants, the rate of CP attributable to intrapartum asphyxia is between 20 - 24% but the level of evidence to support this conclusion is weak.

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APPENDIX A: Screening tool for inclusion of studies

Study	pH<7	A5<7	NE/H	MOD	CP	GA>37
Yudkin et al 1995	√	√	√	√	√	√
Korst et al 1999	√	√	√	√		√
Blair et al 1988		√	√		√	
Rosenbloom 1994		√	√		√	√
Thornberg et al 1995		√	√		√	√
Hagberg et el 2005		√	√		√	√
Gurbuz et al 2006		√	√		√	√

Appendix A : KEY TO TABLE

- Ph < 7.0 or base excess > = 12.
- 5 minute Apgar score of < 7.
- Moderate or severe neonatal encephalopathy/HIE.
- Multi Organ Dysfunction (MOD).
- Cerebral palsy – spastic, dyskinetic or mixed.
- Gestational age >37 weeks.

Summary:

1. Only 2 studies (Yudkin 1995, Korst 1999) matched all four criteria as set out by ACOG.
2. Korst study did not look at CP as an outcome in his study and thus excluded.
3. Five studies conformed to the criteria of Apgar score of <7 at 5 minutes and NE/HIE.
4. Blair 1988 did not report on full term infants, but rather on birth weights at 1500g - 2500g. (excluded)
5. Thornberg 1995 reported on birth asphyxiated infants that later developed CP and the study objectives were not relevant to this review.(excluded)
6. Hence, only 4 studies have been entered into the review.

Rosenbloom 1994

Yudkin et al 1995 (part 2)

Hagberg et al 2005

Gurbuz et al 2006

APPENDIX B: Data extraction form for CP attributed to intrapartum asphyxia

Study ID# 7596893 PubMed	Authors name: Yudkin PL, Johnson A , Clover LM , Murphy KW	Journal : Paed Perinatology Epidemiol
Title : Assessing the contribution of birth asphyxia to cerebral palsy in term singletons Data Extractor  MN	<u>Descriptive data</u> Number of subjects included in study : 173 Age : 0- 5 years Sample size : 166 Follow up period : 5years	<u>Percentage / type of CP</u>  Spastic 100 % ☐ Dyskinetic ☐ Tetraplegic Other _____
Year of Publication  1995	<u>Outcomes :</u> Cerebral palsy Developmental delay Visual impairment Seizures Neonatal encephalopathy	Proportion of CP due to intrapartum asphyxia. 20% Neonatal mortality rate (neonates with asphyxia that died.) 1/2800 (17.4%) 95% CI 5.0, 38.8 Frequency of CP : 2.6/1000
Language of Publication  English	<u>Key results :</u> Spastic quadriplegia	<u>Confounding Factors:</u> none
Country of Publication  England		
Study design  Cohort		

Study ID# 8157150 PubMed	Authors name: Rosenbloom L	Journal : Dev Med Child Neuro
Title : Dyskinetic cerebral palsy and birth asphyxia Data Extractor 🇬🇧 MN	<u>Descriptive data :</u> Number of subjects included in study 115 Age : 0-5 years Sample size : 17 Follow up period : 17 year period	<u>Percentage / type of CP</u> ☐ Spastic 🇬🇧 Dyskinetic 58% ☐ Tetraplegic Other :
Year of Publication 🇬🇧 1994	<u>Outcomes :</u> Cerebral palsy Neonatal encephalopathy	Proportion of CP due to intrapartum asphyxia 58% Neonatal mortality rate (neonates with asphyxia that died.) Not measured Frequency of CP : Not measured
Language of Publication 🇬🇧 English		
Country of Publication 🇬🇧 England	<u>Key results :</u> Dyskinetic CP	<u>Confounding Factors:</u> Breech delivery
Study design 🇬🇧 Cohort		

Study ID# 11332166	Authors name: Hagberg B, Hagberg G, Beckung E	Journal : Acta Paediatr
Title : Changing panorama of cerebral palsy in Sweden: Prevalence and origin in the birth year period 1991-94 Data Extractor  MN	Descriptive data Number of subjects included in study 241 Age : 0 - 4 years Sample size : 132 Follow up period : 4 years	Percentage / type of CP  Spastic 41%  Dyskinetic 59% O Tetraplegic Other : Ataxic Diplegic Hemiplegic
Year of Publication  2005	Outcomes : Cerebral palsy Seizures	Proportion of CP due to intrapartum asphyxia. 24.2% (>37 weeks) Neonatal mortality rate (neonates with asphyxia that died.) Not reported Frequency of CP : 1.24 /1000 (as reported)
Language of Publication  English	Key results : Spastic quadriplegia Spastic hemiplegia Spastic Diplegia Dyskinetic	Confounding Factors: Placenta abruption Congenital sepsis Maternal disease Uterine rupture Diabetic mothers
Country of Publication  Sweden		
Study design  Cohort		

Study ID# 16690507 PubMed	Authors name: Gurbuz A, Karateke A, Yilmaz U, Kabaca C	Journal : The Journal of Maternal-Fetal and Neonatal Medicine
Title : The role of perinatal and intrapartum risk factors in the etiology of cerebral palsy in term deliveries in a Turkish population Data Extractor  MN	Descriptive data Number of subjects included in study 167 Age : 2- 10 years Sample size : 101 Follow up period : 10 years	Percentage / type of CP  Spastic 52.5%  Dyskinetic 7.9% O Tetraplegic Other :Mixed CP – 25.7% Ataxic – hypotonic CP 13.9%
Year of Publication  2006	Outcomes : Cerebral palsy Neonatal encephalopathy	Proportion of CP due to intrapartum asphyxia 20.8% (>37 weeks) Neonatal mortality rate (neonates with asphyxia that died.) not measured Frequency of CP : 0.2 -2.5% (as reported)
Language of Publication  English		
Country of Publication  Turkey	Key results : Spastic quadriparesis Spastic hemiparesis Hypotonic CP Mixed CP Dyskinetic CP	Confounding Factors: Placental abruption Congenital sepsis
Study design  Case control		

APPENDIX C: Characteristics of excluded studies

Author	Year	pH<7	A5<7	NE/ HIE	CP	MOD	GA >37
Low et al	1975	✓	✓				
Scott et al	1976				✓		✓
Low et al	1978		✓	✓			✓
Mcdonald et al	1980						✓
Finer et al	1981		✓	✓			✓
Paneth et al	1983		✓		✓		
Koppe et al	1984				✓		✓
El Rafai et al	1984		✓		✓		
Nelson et al	1986				✓		
Levene et al	1986		✓	✓	✓		✓
Shields et al	1988	✓			✓	✓	✓
Ellenberg et al	1988	✓			✓		
Laing et al	1988	✓	✓			✓	
Grant et al	1989						

Halligan et al	1992	✓	✓	✓			✓
Rosen et al	1992				✓		
Blair et al	1993		✓				✓
Naulty et al	1994			✓	✓	✓	✓
Gaffney et al	1994			✓	✓		✓
Gaffney et al	1994				✓		✓
Gaffney et al	1995		✓	✓	✓		✓
Stewart et al	1995						✓
Mane et al	1995				✓		✓
Wolf et al	1998		✓				✓
Badawi et al	1998	✓	✓	✓			
Ellis et al	1998				✓		✓
Nelson et al	1998				✓		
Ellis et al	1999			✓			✓
Low et al	2001	✓	✓			✓	✓
Moster et al	2001		✓				✓

Jerneck et al	2001		✓		✓		✓
Walstab et al	2002				✓		✓
Kaye et al	2003		✓				✓
Wu et al	2004			✓	✓		
Badawi et al	2005			✓	✓		✓
Hogan et al	2006	✓					✓
Wu et al	2006				✓		✓
Samashima et al	2007	✓			✓		✓

Key:

- Ph < 7.0 or base excess ≥ 12 .
- 5 minute Apgar score of < 7.
- Moderate or severe neonatal encephalopathy/HIE.
- Multi Organ Dysfunction (MOD).
- Cerebral palsy – spastic, dyskinetic or mixed.
- Gestational age >37 weeks.

Summary:

38 studies were entered into Appendix C and were excluded from this review. A further 3 studies, Korst 1999, Blair 1988 and Thornberg 1995 were entered into Appendix A and were also excluded.

In total 41 studies remained excluded from this review.

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

R14/49 Nalla

CLEARANCE CERTIFICATE

PROJECT

PROTOCOL NUMBER M070605

The Contribution of Intrapartum Asphyxia
to the Development of Cerebral Palsy in
full term infants: A systematic review

INVESTIGATORS

Dr M Nalla

DEPARTMENT

Department of Paediatrics

DATE CONSIDERED

07.06.29

DECISION OF THE COMMITTEE*

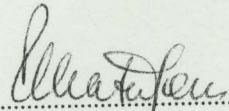
APPROVED UNCONDITIONALLY

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

DATE

08.01.30

CHAIRPERSON


(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof KD Bolton

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES