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CHORIOAMNIONITIS AND CEREBRAL PALSY

By

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ABSTRACT

CHORIOAMNIONITIS AND CEREBRAL PALSY

By

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Preterm infants (less than 37 gestational weeks) constitute more than one third of all new cases of cerebral palsy (CP). Seven studies were reviewed with a meta-analysis to evaluate the association between chorioamnionitis and CP. Unlike a previous meta-analysis by Wu, bias from misclassification was minimized and homogeneity was achieved by dividing articles into two groups based on the method of exposure ascertainment: clinical chorioamnionitis and clinicians' impression of chorioamnionitis. Clinical chorioamnionitis was positively associated with CP (OR=1.79, 95% CI 0.96-3.36). Clinicians' impression of chorioamnionitis showed a strong association with CP (OR=3.83, 95% CI 2.27-6.45).

The association between chorioamnionitis and CP in the New Jersey Neonatal Brain Hemorrhage (NBH) data was tested in a prospective study design. Comparison was made between two cohorts of infants divided according to gestational age above and below 31 weeks. Among four definitions of clinical chorioamnionitis used in the recent literatures, the one most strongly associated with CP was discharge diagnosis of chorioamnionitis in the cohort of infants above 31 weeks (OR=6.61, 95% CI 1.61-27.21), while abruptio placenta played a more important role in infants below 31 weeks after controlling for infection, race, route of delivery, SGA, and preterm labor (OR=4.24, 95%CI 1.34-13.47).

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I pay my sincere thanks to all teachers of my last six years. Without them I would not be able to come out of my small box and see the new vista that is so beautiful and challenging.

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To Ms. Tammy Salman, Bonnie Hissong, Michelle Garn, and Joy DeBoer I owe much because without them I could not have been able to attend classes and see patients at the same time.

To my wife, Sook Young, I owe more than I can express for her encouragement, kind advices, and patience.

My parents instilled the dream when I was a kid that I could do whatever I want to do in my life. My dad trusted me in this more than anybody.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

GLOSSARY

Abruptio:	abruptio placenta: premature separation of placenta
CP:	cerebral palsy: a nonprogressive impairment of motor function
DCP:	disabling CP: inability to walk ten steps unaided by 2 years of age
FEM:	fixed effects model: a model for a meta-analysis with homogeneity
GA:	gestational age: age of fetus in weeks at birth
IUGR:	intrauterine growth restriction: infants weighing less than tenth percentile of weight for that GA
IVH:	intraventricular hemorrhage
LMP:	last menstrual period: the first day of last regular period
LBW:	low birth weight: infants born with birth weight less than 2,500gm
NBH:	New Jersey Neonatal Hemorrhage study
PEL/VE:	parenchymal lesion/ventricular enlargement
PVL:	periventricular leucomalacia
PROM:	premature rupture of membrane
Previa:	placenta previa: placenta located near or over internal cervical os of pregnant uterus
REM:	random effects model: a model for a meta-analysis with heterogeneity
SGA:	small for gestational age: infants weighing less than tenth percentile of weight for that GA
VLBW:	very low birth weight: infants born with birth weight less than 1,500gm
WMD:	white matter damage: parenchymal bleeding of germinal matrix in fetal brain

INTRODUCTION

The prevalence of cerebral palsy (CP) has not changed over past two decades and remains about 2.0 per 1000 live births [1]. The incidences of preterm births and of very low birth weight (VLBW) (infants weighing less than 1500g) are 8.7-10.5% and 1.17-1.24 % respectively [2] [3]. There have been no significant changes in the birth rate of VLBW infants or in the incidence of CP among these infants (7.5%-8.5% among surviving VLBW infants) [4]. Of the approximately 4 million live births annually, about 50,000 VLBW infants are admitted to neonatal intensive care units. Since the introduction of steroids and surfactants in the 1980s, there has been a continual decline in the mortality rate, so that approximately 85% of infants between 700 to 1500g birth weights now survive the neonatal period [5]. Now more than one third of CP (3,100 of 8,000 annual CP) comes from VLBW infants. VLBW infants are 27 times more likely to have CP than full-term infants [6]. Without improvement of CP incidence in this birthweight group, it will be difficult to realize significant progress in lowering the overall incidence of CP in this country. The annual cost of CP is $2.4 billion, which represents one third of the cost of the 18 most common birth defects [7]. Indirect expenditures include the life long care of CP which burdens the family, the health care industry, and society.

One factor that seems to play an important role in CP among VLBW infants is chorioamnionitis, whether this be via an association with clinical chorioamnionitis or histological chorioamnionitis, or possibly via a combined effect of clinical and histological infection. The association of chorioamnionitis and CP is significant in some, but not in all studies. Some studies reported minimal or no association between

chorioamnionitis and CP [8, 9]. Others showed a strong association [10, 11]. This inconsistency may come from considerable methodological differences brought about by various researchers' differing definitions of chorioamnionitis. Because clinical chorioamnionitis is diagnosed based on signs and symptoms of infection recorded in medical records, some authors select some of them or others use all before they include them as an exposure. Whereas some studies [8, 12] used only fever for the diagnosis of chorioamnionitis, others [13-15] added clinical signs such as tachycardia, uterine tenderness, and tachycardia for the criteria of chorioamnionitis.

In numerous studies that have researched a possible association between chorioamnionitis and CP in preterm infants, infants were categorized by their birth weights alone 1500g or less [8, 14, 16-18]. This method of sampling by weight alone could oversample older gestational ages (GA) infants with intrauterine growth restriction (IUGR). Thus categorization by birthweight alone might produce cohorts that are not optimal for causation studies [19]. Studies have suggested that infants less than 30 to 32 weeks gestational age (GA) have higher incidences of chorioamnionitis, premature rupture of membrane (PROM), and intraventricular hemorrhage (IVH), than those of more than 32 weeks GA. Chorioamnionitis is more common when PROM occurs before 30 to 32 weeks than later in pregnancy [20]. PROM occurred in 27-36% of infants born before 32 weeks and in 3-5% of those above 32 weeks [21, 22]. Not all authors agree with this large difference in the incidence of PROM by GA, but an inverse relation between GA and PROM has been recognized in several studies[22-24]. The rate of IVH diminishes sharply as gestational age increases, with an incidence of less than 1% at gestational age of 32 weeks and older [25].

Few studies have compared the strength of association between infants born before 31 weeks and older GA groups. No studies have tested the effect of this association using different criteria for diagnosis of chorioamnionitis to the same cohort to compare the strength of association by diagnostic criteria. By conducting studies of premature infants by gestational week (below 31 and above 31 weeks) the confounding effect of GA and IUGR will be reduced for analysis. Differences of association in the two GA cohorts could help us to elucidate possible causal factors of disabling CP (DCP).

The objective of the current study is to test the null hypothesis that the incidence of DCP is unrelated to chorioamnionitis after adjustment of relevant confounders in both infants above and below 31 weeks GA. This paper consists of two parts: part one describes a meta-analysis that is conducted to summarize the association of chorioamnionitis and CP in recent clinical and epidemiological researches. In part two, using the data from New Jersey Neonatal Brain Hemorrhage (NBH) study of low birth weight infants less than 2000g, the association of DCP and clinical chorioamnionitis is tested in two cohorts, stratified by gestational age less than 31 weeks (below 31 weeks) and equal to and above 31 weeks (above 31 weeks). Clinical chorioamnionitis using four different definitions commonly used in recent studies is analyzed to compare the strength of association by diagnostic criteria. Finally, the meta-analysis is re-run with the inclusion of the NBH data.

PART ONE

A Systematic Literature Review: Meta-Analysis

A meta-analysis was conducted to acquire an understanding of the association between cerebral palsy and chorioamnionitis. Over the past two decades, several epidemiological studies have examined the association between cerebral palsy and intraamniotic infection. Varying definitions, different modeling, various cohorts and location differences were noticeable in the several studies reviewed. Some recent case-control and cohort studies have reported positive associations between cerebral palsy and chorioamnionitis [10, 11, 13, 15, 26]. No association was shown in other studies [18, 27]. Thus it is still unclear whether there is an elevated risk for CP among women who are diagnosed with chorioamnionitis. It is also difficult to distinguish whether the risks of CP are associated with the exposure to clinically obvious chorioamnionitis, to histologically determined chorioamnionitis, or to combined (clinical and histologic) chorioamnionitis. It appears that differences in study designs and consequent differences in biases may influence the results of the studies and account for discrepancies in the literatures.

To acquire a better understanding of the nature of the reported association between cerebral palsy and chorioamnionitis, a meta-analysis was conducted including all studies published from 1966 to December 2000.

Methods

Study Identification

Studies included in this review were identified from a larger subset of all identified studies of cerebral palsy-related etiology, epidemiology and prenatal risk factors for chorioamnionitis. This larger pool of studies was identified by cross-referencing the following Medical Subject Headings (MeSH) terms using MEDLINE from 1966 to 2000—*cerebral palsy, chorioamnionitis* with the following MeSH terms-*etiology, epidemiology.* In addition, every citation for cerebral palsy from January 1990 to 2000 was examined and the abstracts of potentially relevant citations were reviewed on line.

Study Selection

The following selection criteria were used to identify studies for inclusion in this analysis.

1. Study design: Included studies were required to be either case control studies, nested case control studies, or cohort studies; the relative risk or odds ratio with 95% confidence interval was provided or could be calculated from the data presented in the paper.

2. Outcome: cerebral palsy

3. Exposures: Clinical chorioamnionitis, histological or microbiological chorioamnionitis, or the attending (discharge) diagnosis of chorioamnionitis

4. Studies including singletons of gestational week less than or equal to 35 weeks, or birth weight less than or equal to 1,500g

5. Excluded Studies: unspecified gestational weeks, gestational week greater than 35, and if multiple births were included in the study.

Through the literature search in MEDLINE (1966-2000), I identified a total of 128 English language studies with titles that discussed etiology or risk factors of cerebral palsy or periventricular leucomalacia (PVL) (believed to be a precursor of cerebral palsy in premature infants); 1350 studies had 'chorioamnionitis' in the titles, or abstracts, or the medical subject headings. Of 15 initially identified publications that discussed the association between chorioamnionitis and cerebral palsy or PVL, one study (Itakura)[28] was excluded because its primary hypothesis was to estimate the timing of brain damage involved in the onset of PVL in the perinatal period and analyzed neonatal electroencephalograms. One article (Eschenbach) [29] was an editorial and therefore excluded from this review. One study (Grether) [30] was excluded because it was in infants of normal birth weight. Two studies (Wu and Vigneswaran) [31, 32] were excluded due to publication type- one was a meta-analysis, the other a review paper. The outcome variable in Verma U [27] and Redline RW [33] papers were IVH and PVL and thus were excluded from the study. One paper (Perlman) [34] had PVL as the main outcome variable. We decided to focus only on CP as the outcome variable for the meta-analysis, and did not include Perlman's study. For O'Shea et al [15, 17] and Yoon et al [26, 35] published papers that were updates of previously reported studies, only the paper with the most inclusive study population was selected, i.e., O'Shea 1998 and Yoon BH 2000 [15, 26]. Table-1 lists these 10 publications as reviewed but excluded from the meta-analysis. The remaining 5 independent papers [8, 10, 15, 18, 26] reported results pertaining to chorioamnionitis as the exposure of interest and cerebral palsy as the main outcome variable, and were included in the meta-analysis.

Table 1: Publications reviewed but excluded from the meta-analysis

Study	Publi-cation Year	Reasons for exclusion
Itakura-A et al	1996	Primary hypothesis was not CP and chorioamnionitis
Eschenbach-DA et al	1997	Editorial type of publication
Grether-JK et al	1997	Study in normal birth weight infants
Wu YW et al	2000	A meta-analysis
Vigneswaran R et al	2000	A literature review paper
Yoon BH et al (1)	1997	Gestational age up to 35 weeks
Verma U et al	1997	Outcome in periventricular leucomalacia (PVL)
Redline RW et al	1998	Outcome in PVL, the same cohort of Wilson-Costello
O'Shea et al	1997	Cases from 1978-89
Perlman JM et al	1996	Outcome variable was PVL

Two papers, Cooke's and Allan's, were cited in articles that were selected for this study (Table 2), although they had not been picked up through Medline key words search, so they were included in this review. Thus, in total, seven studies (Table 2) constitute the meta-analysis throughout this paper.

Table 2. Studies selected for the meta-analysis

Study	Study year	Publication Year	Study Design	GA week/ Birth Weight	# of cases	# of controls
Murphy DJ	1984-90	1995	case-control	<32 wks	59	234
Grether JK	1983-85	1996	case-control	<1500 g	42	75
Wilson-Costello	1983-91	1998	case-control	<1500 g	50	50
O'Shea	1986-93	1998	case-control	500-1500 g	62	124
Cooke RW	1980-86	1990	case-control	<1500 g	81	81
Yoon BH	1993-95	2000	cohort	26-35 wks	14	109
Allan WC	1989-92	1997	cohort	600-1250 g	36	339

Data Extraction

Information was assembled in a standard form, including sample size in each case or control group and the exposure/outcome of interest. The following data were abstracted onto the standardized form: publication year, years of study, gestational age, method of obtaining exposure information, definition of chorioamnionitis, definition of cerebral palsy, minimum age at diagnosis of cerebral palsy, numbers permitting me to calculate OR or RR; source of cases and controls, and extent of controlling for potential confounding.

Statistical Analysis:

Meta-Analyst software [36] was used to combine all studies with both the DerSimonnian and Laird random effects method (D&L REM) and the fixed effects method (M-H FEM). The pooled risk estimates for these 7 studies are summarized by weighted averages in which the weight is the inverse of the variance of the estimate. A heterogeneity test Q-statistic, as well as random-effects and fixed-effects summaries, was computed. Heterogeneity and homogeneity describe the degree of between-study variability among studies. In order to test heterogeneity the Q-statistic and P value were calculated. If $P < 0.05$, then there is significant heterogeneity. In such case we use random effects models for a meta-analysis, which considers both between-study and within-study variability. The fixed effects model considers only within-study variability, and can be used when there is significant homogeneity ($P > 0.05$).

Description of studies

The general characteristics of the seven studies are summarized in Table 3.

The 7 studies included 1356 subjects in total: 344 CP patients, and 1012 non-CP patients. Years of research were in the 1980s or early 1990s. The study designs and settings were slightly different. Murphy [10] and Grether [8] sought information from local registries and performed case-control studies in Oxford, UK and in the California Bay Area counties, respectively. O'Shea's [15] and Allan's [37] studies were in multi-site tertiary obstetric referral centers. The Wilson-Costello's [18] and Yoon's [26] studies were at University Hospital for Women in Cleveland Ohio, and at university hospitals in Seoul Korea. Cooke's study [9] was a nested case-control study conducted in Mercy Regional Neonatal Intensive Care Unit at University of Liverpool, UK.

Table 3. Characteristics of seven studies comparing chorioamnionitis and CP

Author	Murphy	Grether	Wilson-Costello	O'Shea	Cooke	Yoon BH	Allan WC
Yrs of study	1984-90	1983-85	1983-91	1986-93	1980-86	1993-95	1989-92
Area, Country	Oxford, England Registry	San Francisco Bay area, Registry	Cleveland, Tertiary Center	North Carolina, Tertiary Center	Liverpool, England, Regional NICU	Seoul, Korea, Tertiary Center	Portland. RI. Conn. Tertiary Center.
# of preterms	638	-	1050	1238	1142	172	431
Total survived	538	-	839	984	761	-	-
# of infants examined	533	881	764	815	761	123	381
# of CP cases	59	42	50	62	81	14	36
# of Controls	243	75	50	124	81	109	339
amnionitis in CP (%)	10(17%)	23(54%)	11(22%)	12(23%)cl 14(67%)hi	17(21%)	2 (14%)cl 10(82%) hi	10(19%)
amnionitis in control (%)	8 (3%)	42(56%)	6(15%)	11(10%)cl 17(61%)hi	6(7%)	7 (6%)cl 44(42%) hi	26(8%)
Age of CP diagnosed	3 and 5 yrs	3 yrs	20 months	1yr	2 yrs	3 yrs	36 months
Year of publication	1995	1996	1998	1998	1990	2000	1997
Study design	Case-control	Case-control	Case-control	Case-control	Case-control	Cohort	Cohort

Note: cl=Clinical chorioamnionitis; hi=Histologic chorioamnionitis

The main criteria of eligibility used in these 7 studies were roughly the same. Subjects were eligible for inclusion if they were singleton infants under 35 gestational weeks or with birth weight equal to or less than 1500 g singleton infants. All seven studies excluded infants of multiple births because they pursue different physiological maturation from singleton infants. Gestational weeks or birth weight were not significantly different in CP and non-CP groups.

Diagnostic criteria for chorioamnionitis in each study are summarized in Table-4. The diagnostic criteria for clinical chorioamnionitis used in 4 studies (Grether, Wilson-Costello, Cooke, Yoon) [8, 9, 18, 26] were, in principle, the same. They were based on 6 clinical symptoms or signs, either alone or in combination. Signs included were maternal fever during labor, uterine tenderness, maternal leukocytosis, malodorous amniotic fluid, and maternal or fetal tachycardia. However, other three authors combined clinical and histological signs of infection. Murphy [10] included histologic and microbial chorioamnionitis for exposure. Allan [37] used attendings' diagnosis of chorioamnionitis for exposure. O'Shea included 23 cases of attendings' diagnosis of chorioamnionitis that included histologic findings, antibiotic use, and clinical signs of chorioamnionitis. Therefore, Murphy, O'Shea, and Allan [10, 15, 37] used similarly defined chorioamnionitis as their exposures, because discharge or attendings' diagnosis of infection included clinical, histologic and microbial findings.

CP was the main outcome of interest among 7 studies. Grether [8] got CP information from postneonatal medical and service agency records and from the birth defect registry, and excluded nondisabling CP. The definition of CP used in the registry in Murphy's study [10] was 'permanent impairment of voluntary movement or posture'.

Table 4 Diagnostic Criteria for Clinical Chorioamnionitis in each study

Clinical symptom/sign	Murphy	Grether	Wilson-Costello	O'Shea	Cooke	Yoon	Allan
Maternal fever	>=2 clinical signs or microbiological or histologic evidence	Fever>38 during labor or foul smelling discharge	>37.8 + 2 signs or >38.3 + 1 sign	PROM + 2 sign, or attendings' diagnosis of chorio-amniotis	PROM + 1 sign or more	37.8 + 2 of signs	Attending' diagnosis of chorio-amnionitis
Uterine tenderness							
Leukocytosis> 11000							
Foul smelling discharge							
Maternal Tachycardia >100							
Fetal tachycardia >160							

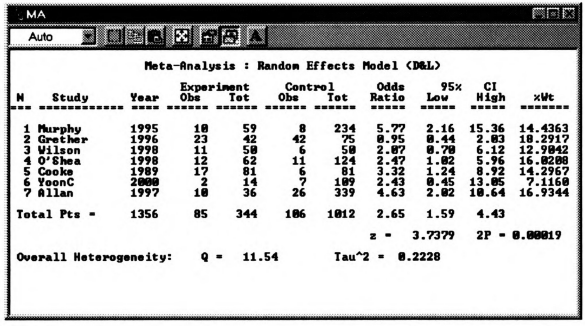
Cooke [9] evaluated the degree of disability and included only CP with noticeable disability. Children with a diagnosis of 'clumsiness' were not included. Allan [37] included the CP subtypes, diplegia, hemiplegia, and tetraplegia. Wilson-Costello [18] studied 72 infants with classically defined CP (50) as well as those with nondisabling CP (22). 50 infants with CP were included in this study. O'Shea [15] diagnosed CP with a multidisciplinary examination at 1 year adjusted age. Yoon [26] did not mention degree of disability for inclusion. Ages of diagnosis of CP in these studies were all under 5 years.

Results

1) Association between chorioamnionitis and CP in preterm infants in 7 selected studies

Results from Random Effects Model (REM): Pooled OR=2.65 (95% CI: 1.59-4.43).

The Q-statistic showed that the pooled analysis was heterogeneous (Q=11.54, p<0.025).



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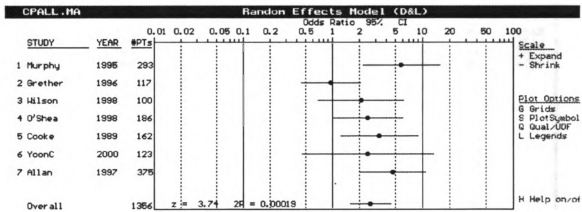
Meta-Analysis : Random Effects Model (D&L)

N	Study	Year	Experiment Obs	Experiment Tot	Control Obs	Control Tot	Odds Ratio	95% CI Low	95% CI High	xWt
1	Murphy	1995	10	59	8	234	5.77	2.16	15.36	14.4363
2	Grether	1996	23	42	42	75	0.95	0.44	2.03	18.2917
3	Wilson	1998	11	58	6	58	2.07	0.70	6.12	12.9842
4	O'Shea	1998	12	62	11	124	2.47	1.02	5.96	16.0288
5	Cooke	1989	17	81	6	81	3.32	1.24	8.92	14.2967
6	YoonC	2000	2	14	7	109	2.43	0.45	13.05	7.1160
7	Allan	1997	10	36	26	339	4.63	2.02	10.64	16.9344
Total Pts =		1356	85	344	106	1012	2.65	1.59	4.43	

z = 3.7379 2P = 0.00019

Overall Heterogeneity: Q = 11.54 Tau^2 = 0.2228

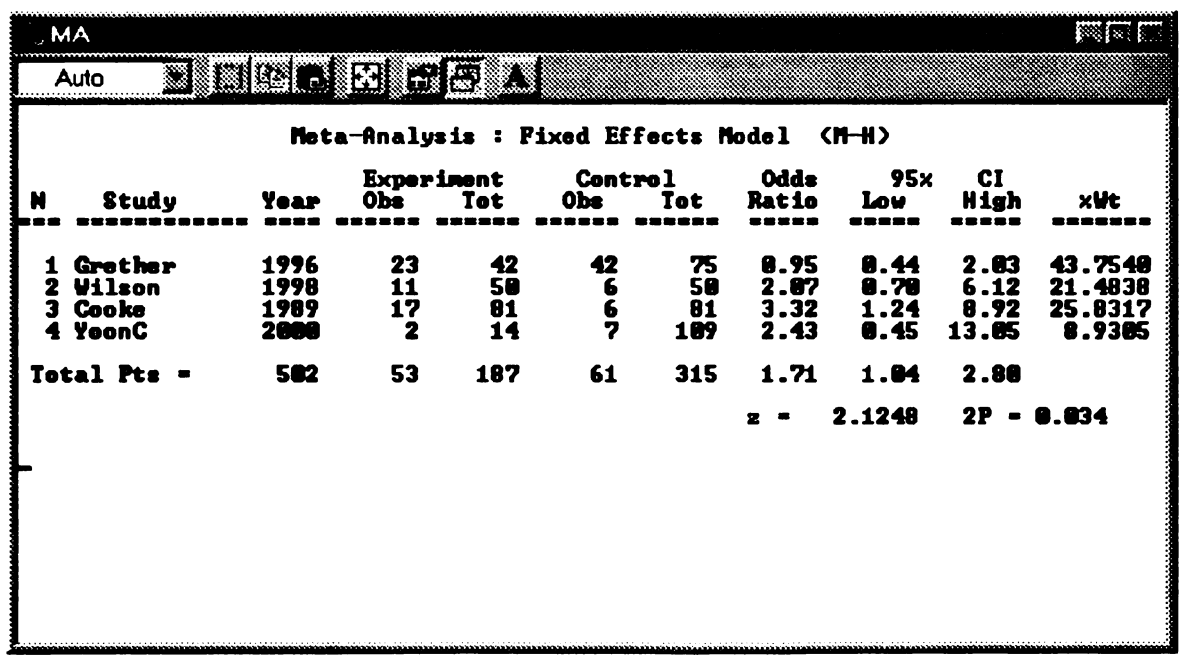
Results based on REM presented in graph:



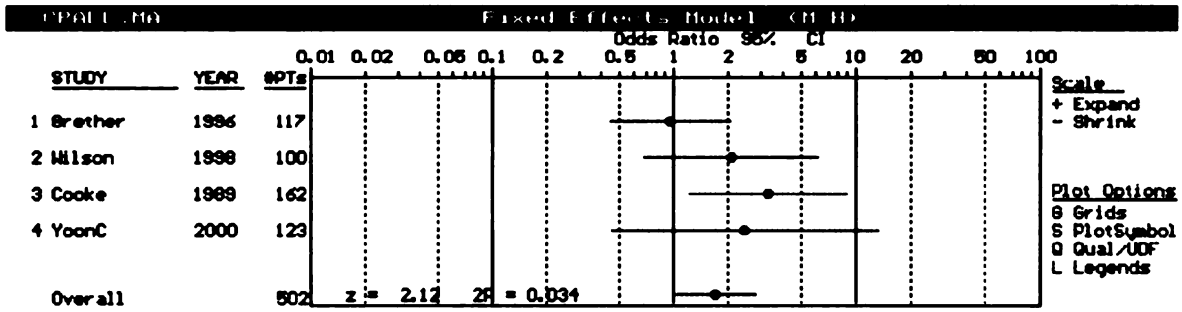
The test of heterogeneity (Q=11.54 p <0.025) indicated that the 7 studies were significantly heterogeneous. Some of the heterogeneity seemed likely to come from using different criteria of exposure. Murphy, O'Shea, and Allan had different definitions of infection, which were more sensitive than the remaining 4 studies. They were based on combination of clinical and histologic signs/symptoms. Therefore, I re-ran the meta-analysis excluding the Murphy, O'Shea, and Allan studies. The meta-analysis results are as follows:

2) Association between clinical chorioamnionitis and CP in preterm infants in 4 selected studies

Results from Random Effects Model among 4 studies: Pooled OR = 1.79 (95% CI: 0.96-3.36). The Q-statistic showed that the pooled analysis is homogeneous (Q=4.30, p>0.20). Therefore, the result from the Fixed Effects Model (FEM) in 4 studies is presented below: Pooled OR = 1.71 (95% CI: 1.04 – 2.80). A weak positive association was noted from the pooled results.



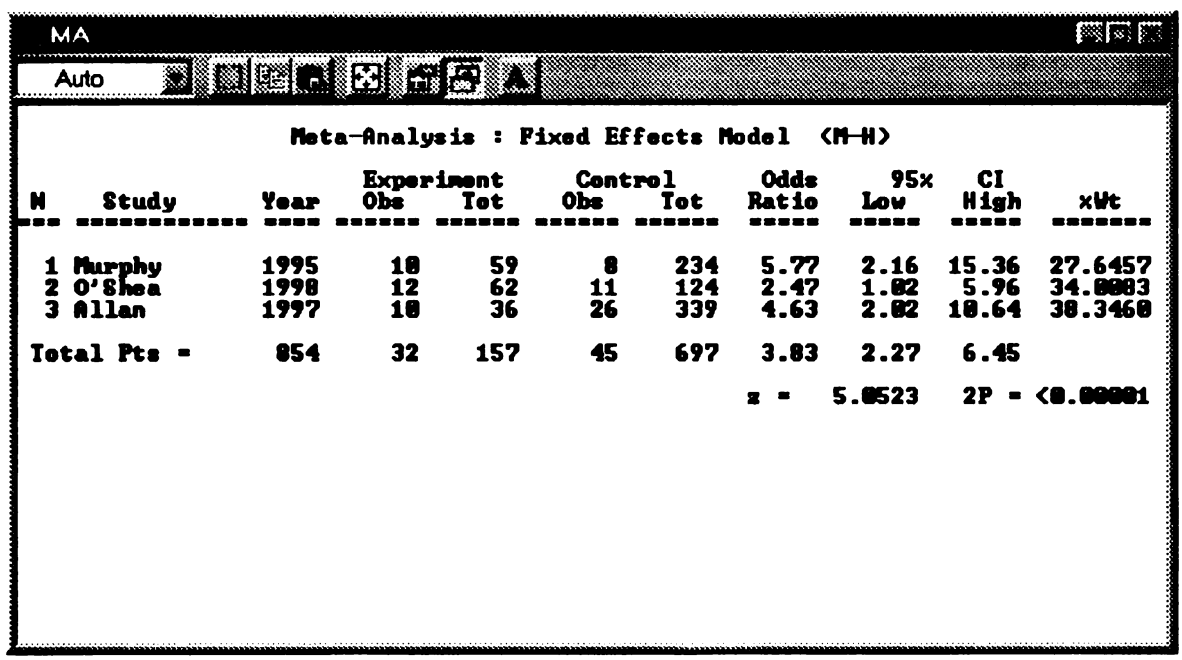
Results based on FEM among 4 studies in graph:



3) Association between 'combined' chorioamnionitis and CP in preterm infants

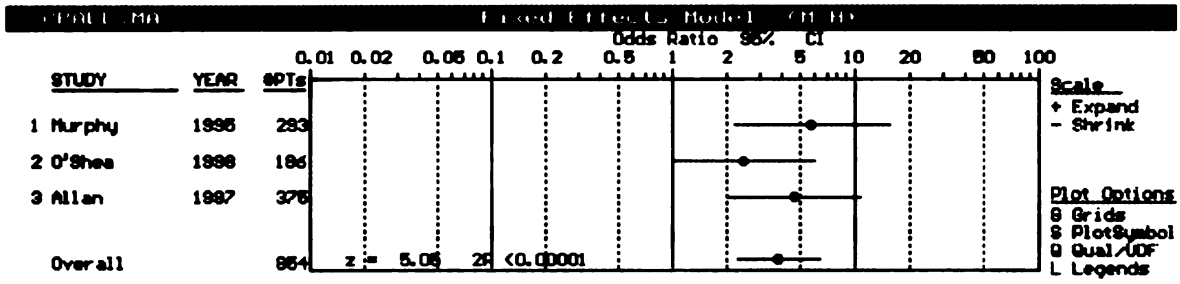
(Murphy, O'Shea, and Allan's studies)

The test of homogeneity showed that the other 3 studies were also homogeneous (Q=1.81, p=0.20). The results from the fixed effects model showed OR=3.83 (95%CI 2.27-6.45) and a significant association between CP and infection.



N	Study	Year	Experiment Obs	Experiment Tot	Control Obs	Control Tot	Odds Ratio	95% CI Low	95% CI High	xWt
1	Murphy	1995	18	59	8	234	5.77	2.16	15.36	27.6457
2	O'Shea	1998	12	62	11	124	2.47	1.02	5.96	34.8883
3	Allan	1997	18	36	26	339	4.63	2.02	10.64	38.3460
Total Pts =		854	32	157	45	697	3.83	2.27	6.45	
							z =	5.0523	2P =	<0.00001

In graph:



In summary, the meta-analysis with all 7 studies showed that the overall pooled result was statistically heterogeneous ($p<0.025$). The heterogeneity came from large between-study variances. Therefore, the analysis was divided into two halves. The first was restricted to the 4 studies that used only clinical signs and symptoms to determine clinical chorioamnionitis. A weak association was found based on the fixed effects model. The odds ratio was 1.71 and the 95% confidence interval was 1.04 – 2.80. The other half included the studies of Murphy, Allan and O'Shea that were homogeneous. In this group there was a strong positive association between 'combined' chorioamnionitis and CP with an OR=3.83 (95%CI 2.27-6.45).

PART TWO

NBH DATA

Materials and Methods

Study Population

The Central New Jersey Neonatal Brain Hemorrhage Study (NBH study), a multi-center, long-term follow-up study of small infants, enrolled a geographically representative sample of 1,105 live-born infants weighing<=2,000g at birth, a cohort comprising about 85% of all births of that weight born from September 1984 to June 1987 in the central New Jersey counties of Ocean, Monmouth, and Middlesex. Their weight ranged from 501 g to 2,000g and gestational ages from 22 to 41 weeks. Of these 167 died in the hospital and 37 died later, leaving 901 infants available for follow-up examination at age two. Twenty-six percent of the cohort was African-American and 25% were multiple births. In this study, prenatal and postnatal records were abstracted and the mother was interviewed shortly after birth. Information about prenatal exposures including smoking, alcohol and medications, illness, behaviors, and reproductive history and practice was obtained and recorded. Data were abstracted in detail from mothers' prenatal records and hospital charts [38, 39].

Gestational age in the NBH study was calculated from the last menstrual period (LMP) as reported at a postpartum interview or as abstracted from the prenatal record if there was no interview. When there was dating information from an ultrasound before 18 weeks, the ultrasound dates were used only if they were more than 14 days discrepant from the menstrual dates. Postnatal GA assessments based on physical or neurological criteria were not used [40].

Follow-up Examination

Age at the time of assessment was two years following the expected date of confinement (EDC) based on the LMP of mothers. The examination took place at one of two testing sites in central New Jersey or at the home of the participants. Of the 901 survivors at age two, 10 children were adopted out, 67 moved out of state, and 103 children could not be located. The remaining 721 (80%) children were examined, and clinical information was obtained by mail or phone interview of parents on 56 children known to have moved out of state, yielding a total follow-up rate of 86% (n=777).

Examination was focused on the detection of major developmental handicaps. Motor status was assessed by a specially trained nurse or nurse practitioner who examined the child's motor tone, extrapyramidal movements, and tendon reflexes in all limbs. If she could not classify the child as clearly normal in motor function, the child was referred to one of four consultant child neurologists. For the purpose of this investigation, very low birth weight infants from twin and other multiple gestations were excluded because morbidities are unique to multiple pregnancies. Similarly, infants with congenital malformations, when information was available, were excluded for this study. The outcomes of interest were CP status assessed at 2 years of age. Criteria for disabling CP (DCP) included the following, in addition to specific neurologic findings [41]:

1. Inability to walk ten steps unaided by 2 years of age;
2. Bayley motor score greater than 1 SD lower than performance score;
3. Receipt of physical therapy for motor disability; and
4. Use of braces or physical assistance devices [38].

Infants with nondisabling CP were included with non-CP infants. Therefore, Non- DCP infants in this study represented the total number of infants with nondisabling CP and without CP.

Study Design and Data Analysis

This is the prospective cohort study for 565 infants divided into two cohorts for the purpose of comparison. 237 singletons whose gestational ages were less than 31 weeks (below 31 weeks) and 328 babies with gestational weeks 31 and greater (above 31 weeks) were studied separately. These two subsets were analyzed for association between CP and chorioamnionitis (Figure 1).

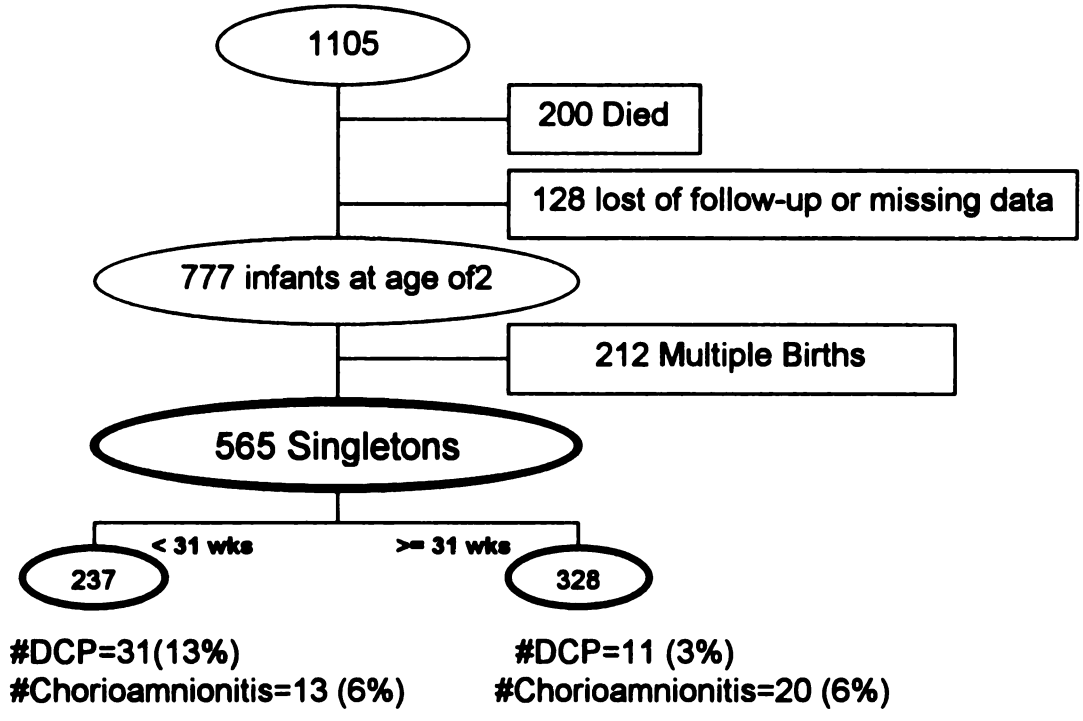


Figure 1: Study Population

Four criteria of clinical chorioamnionitis were used to test its association with disabling CP:

1) The diagnosis of amnionitis from discharge medical charts;

2) O'Shea's definition of clinical chorioamnionitis, i.e. PROM plus two of signs of infection (fever, uterine tenderness, foul fluid, antepartum use of antibiotics), and no other source of fever

3) Grether's criteria, i.e. fever>38 C during labor or foul smelling discharge

4) PROM plus maternal fever (Cooke's criteria)

The association of risk factors with the risk of cerebral palsy and discharge diagnosis of amnionitis was described using the odds ratio (ORs) and 95%confidence limits. Univariate comparisons between two subsets differing in gestational ages were tested using the chi-square test and the Fisher exact test. If one cell in any two by two table was zero, then one was added to all cells to calculate the OR. Spearman correlation analysis was completed to find the importance of variables of chorioamnionitis. The univariate analysis of association of selected variables with DCP in the multiple births was also conducted and presented in the results section. Multiple logistic regression analysis was used to model the association between discharge diagnosis of chorioamnionitis and predictors after adjusting for the risk factors of DCP: race, abruptio, SGA, route of delivery, and preterm labor. To assess the confounding effect among the risk factors of DCP, multiple logistic regression analysis was used to model the association between discharge diagnosis of chorioamnionitis and DCP. The adjusted Odds Ratio was reported for each subset.

Results

1. Univariate analysis of risk factors for cerebral palsy:

Univariate analysis of demographic factors, obstetric factors, and brain damages is shown in Table 5. The demographic characteristics such as sex, race, and level of education were not statistically different between DCP and non-DCP in infants above 31 weeks. The same results were noted for sex and years of education in infants below 31 weeks. CP was significantly more frequent in White infants than in Black infants (OR 4.02, 95% CI 1.18-13.17) in infants below 31 weeks.

In infants below 31 weeks, disabling CP was associated with abruptio placenta (OR=4.17, p=0.001). In infants above 31 weeks, there were associations between DCP and variables related to pregnancy history such as chorioamnionitis diagnosed from discharge medical charts (OR=6.61, p=0.02), but not in infants below 31 weeks (p=0.80). No association was found with status of parity, placenta previa, delivery route, tocolysis, and preterm labor. The associations between CP and preeclampsia were somewhat protective in both subsets (OR=0.17, p=0.06) but were not statically significant (P>0.05). Brain damages diagnosed by ultrasound, both IVH and PEL/VE were strongly associated with CP in all subsets: PEL/VE (OR=14.58, 95% CI 5.98-35.55) and IVH (OR=5.12, 95% CI 2.23-11.72) in infants below 31 weeks, PEL/VE (OR=69.73, 95% CI 13.86-355.02) and IVH (OR=7.11, 95% CI 1.79-29.64) in infants above 31 weeks.

Table 5 Univariate analysis of association of several variables with DCP in singletons

Variable	below 31 weeks		above 31 weeks	
	DCP	No DCP	DCP	No DCP
N	31	206	11	317
Sex				
Male	14	98	6	158
Female	17	108	5	159
	OR=1.10 (0.52 – 2.35)		OR=0.83 (0.25 – 2.77)	
Race				
White	28	144	9	241
Black	3	62	2	76
	OR=4.02 (1.18 – 13.71)		OR=1.42 (0.30 – 6.71)	
Education				
<=12 yr schooling	21	98	3	143
>12 yr schooling	9	80	5	117
	OR=1.90 (0.83 – 4.39)		OR=0.49 (0.11 – 2.10)	
Parity				
<=2	22	145	6	206
>2	8	33	2	57
	OR=0.63 (0.26 – 1.53)		OR=0.83 (0.16 – 4.22)	
Chorioamnionitis				
Yes	2	11	3	17
No	29	195	8	300
	OR=1.22 (0.26 – 5.80)		**OR=6.61 (1.61 – 27.21)**	
IVH				
Yes	19	52	4	37
No	10	140	4	263
	OR=5.12 (2.23 – 11.72)		**OR=7.11 (1.70 – 29.64)**	
PEL/VE				
Yes	17	17	5	7
No	12	175	3	293
	OR=14.58 (5.98 – 35.55)		**OR=69.73 (13.86 – 355.02)**	

(Cont'd)

Variable	below 31 weeks		above 31 weeks	
	DCP	Non-DCP	DCP	Non-DCP
Abruptio				
Yes	9	19	2	31
No	20	176	6	273
	OR=4.17 (1.66 – 10.44)		OR=2.94 (0.57 – 15.18)	
Previa				
Yes	1	12	1	13
No	28	183	7	291
	OR=1.84 (0.23 – 14.67)		OR=3.20 (0.37 – 27.94)	
Route				
Vaginal	17	106	4	148
C-section	14	95	6	161
	0R=0.92 (0.51 – 2.33)		OR= 0.73 (0.20 – 2.62)	
SGA				
Yes	1	18	6	137
No	30	188	5	180
	OR=0.35 (0.04 – 2.70)		OR=1.58 (0.47 – 5.27)	
Tocolysis				
Yes	9	69	0	65
No	22	137	11	252
	OR=0.81 (0.36 – 1.86)		OR=0.32 (0.02-2.43)	
Hypertension				
Yes	2	29	0	103
No	28	170	10	199
	OR=0.42 (0.15 – 1.76)		OR=0.17 (0.01-1.33)	
Preterm Labor				
Yes	15	101	5	132
No	8	65	3	119
	OR=1.21 (0.48 – 3.01)		OR=1.50 (0.35 – 6.42)	

2. Univariate analysis of risk factors for chorioamnionitis:

The rate of infection was not significantly different between whites and blacks in preterm infants ($p>0.10$). The rate of chorioamnionitis in infants with abruptio placenta was not significantly different from those without. SGA and preeclampsia (listed as hypertension in the table) was associated with a decreased risk of chorioamnionitis in infants above 31 weeks (OR=0.13, 95% CI 0.13-0.58).

Table 6 Univariate analysis of several variables with discharge diagnosis of chorioamnionitis in the NBH data

	below 31 weeks		above 31 weeks	
Chorioamnionitis*	present	absent	present	absent
N	13	224	20	308
DCP				
Yes	2	29	3	8
No	11	195	17	300
	OR=1.22 (0.26 – 5.80)		**OR=6.62 (1.61 – 27.21)**	
Sex				
Male	3	109	12	152
Female	10	115	8	156
	OR=0.32 (0.08 – 1.18)		OR=1.54 (0.61 – 3.87)	
Race				
White	7	165	16	234
Black	6	59	4	74
	OR=0.42 (0.13 – 1.29)		OR=1.27 (0.41 – 3.90)	
Education				
<=12 yr schooling	8	111	10	136
>12 yr schooling	5	84	9	113
	OR=1.21 (0.38 – 3.83)		OR=0.92 (0.36 – 2.35)	
Parity				
<=2	11	156	14	198
>2	2	39	5	54
	OR=1.38 (0.29 – 6.46)		OR=0.76 (0.26 – 2.21)	
IVH				
Yes	6	65	4	37
No	7	143	14	253
	OR=1.89 (0.61 – 5.83)		OR=1.95 (0.61 – 6.25)	
PEL/VE				
Yes	3	31	1	11
No	10	177	17	279
	OR=1.71 (0.45 – 6.58)		OR=1.49 (0.18 – 12.24)	

(Cont'd)

	below 31 weeks		above 31 weeks	
Chorioamnionitis*	present	absent	present	absent
Abruptio				
Yes	0	28	2	31
No	13	183	18	261
	OR=0.49 (0.02-3.82)		OR=0.94 (0.21 – 4.22)	
Previa				
Yes	1	12	0	14
No	12	199	20	278
	OR=1.38 (0.17 – 11.53)		OR=.	
Route				
Vaginal	7	116	9	143
C-section	6	103	11	156
	OR=1.04 (0.34 – 3.18)		OR=0.89 (0.36 – 2.21)	
SGA				
Yes	1	18	2	141
No	12	206	18	167
	OR=0.95 (0.12 – 7.76)		**OR=0.13 (0.03 – 0.58)**	
Tocolysis				
Yes	8	70	6	59
No	5	154	14	249
	OR=3.52 (1.11 – 11.14)		OR=1.81 (0.67 – 4.90)	
Hypertension				
Yes	1	30	1	102
No	12	186	19	190
	OR=0.52 (0.06 – 4.12)		**OR=0.10 (0.01 – 0.74)**	
Labor				
Yes	6	110	10	127
No	3	70	8	114
	OR=1.27 (0.31 – 5.25)		OR=1.12 (0.43 – 2.94)	

* Chorioamnionitis = discharge diagnosis of chorioamnionitis by clinicians

3. Univariate analysis in Multiple Pregnancy

Among a total of 280 infants of multiple births, 212 were examined. They represented all multiple births less than 2000g with no stratification in gestational ages (Table 7). The overall incidence of CP in multiple births was higher than in singletons (15% vs. 9.8%). Chorioamnionitis showed a significant association with CP (OR=11.24, 95% CI 1.5-84.9) even though numbers exposed (n=4) were small. Two indicators of brain damage, IVH and PEL\VE, showed strong associations with DCP (OR 23.2, 42.6 respectively). Abruptio placenta was strongly associated with CP as in singletons (OR=8.1, 95%CI 1.25-52.22). One third of multiple births showed intrauterine growth restriction compared with 0.8% in singleton infants below 31 weeks. Preterm labor was more significantly associated with CP than was no preterm labor (OR=8.1, 95% CI 1.04-62.96).

Table 7 Univariate analysis of risk factors with DCP in multiple pregnancy

Variable	Multiple pregnancy	
	DCP	No DCP
N	19	193
Sex		
Male	8	100
Female	11	93
	OR=1.48 (0.26-1.76)	
Race		
White	14	150
Black	5	43
	OR=0.80 (0.27-2.35)	
Education		
<=12 yr schooling	7	47
>12 yr schooling	3	47
	OR=2.33 (0.59-9.57)	

(Cont'd)

Variable	Multiple pregnancy	
	DCP	No DCP
Parity		
<=2 delivers	9	74
>2	1	20
	OR=2.43 (0.29-20.35)	
Chorioamnionitis		
Yes	2	2
No	17	191
	OR=11.24 (1.49-84.85)	
IVH		
Yes	14	31
No	3	154
	OR=23.18 (6.28-85.51)	
PEL/VE		
Yes	10	6
No	7	179
	OR= 42.62 (12.05-150.67)	
Abruptio		
Yes	2	3
No	15	182
	OR= 8.09(1.25-52.22)	
Previa		
Yes	1	0
No	16	185
	OR=21.88(1.44-645.94)	
Route		
Vaginal	3	35
C-section	16	158
	OR=0.85 (0.23-3.06)	
SGA		
Yes	5	66
No	14	127
	OR= 0.69 (0.24-1.99)	
Tocolysis		
Yes	5	131
No	14	62
	OR=0.75 (0.26-2.19)	

Variable	Multiple pregnancy	
	DCP	No DCP
Hypertension		
Yes	1	139
No	18	54
	OR=0.14 (0.01-1.09)	
Preterm Labor		
Yes	16	45
No	1	89
	OR=8.09 (1.04-62.96)	

4. The association between DCP and 4 different definitions of chorioamnionitis

Chorioamnionitis illustrated by 3 of 4 common definitions showed no association with DCP. The exception was the discharge diagnosis of amnionitis, which showed a positive association between CP, but only in the subset of infants above 31 weeks (OR=6.61, 95% CI 1.61-27.21). The results based on O'Shea and Grether definitions were similar in terms of the strength and direction of association. Discharge diagnosis of amnionitis and PROM plus fever provided the same trend of the association. In infants below 31 weeks, a negative association was noted by using the O'Shea or Grether definition (OR=0.54 and 0.57, respectively), while a positive association was found in infants above 31 weeks (OR=1.04 and OR=1.17 respectively). But they were not significant statistically.

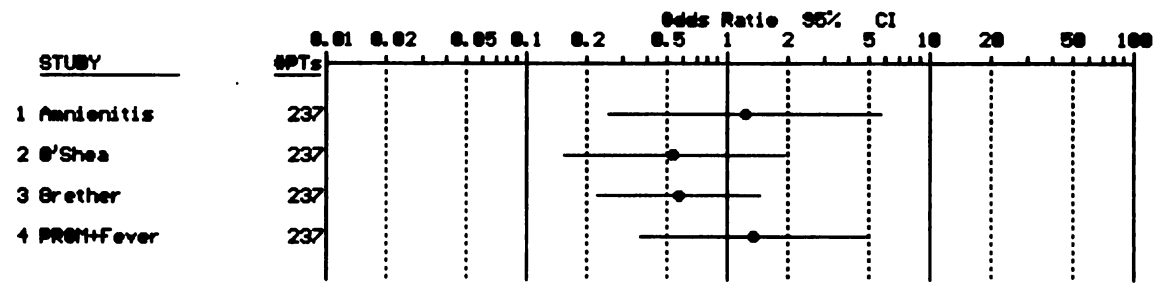
Table 8: The association between CP and using 4 different definitions of chorioamnionitis

	below 31 weeks		above 31 weeks	
	CP (n=31)	No CP (206)	CP (n=11)	No CP (n=317)
Amnionitis	2	11	3	17
	OR=1.22 (0.26 – 5.80)		OR=6.62 (1.61 – 27.21)	
O'Shea	3	34	2	56
	OR=0.54 (0.16 – 1.88)		OR=1.04 (0.22 – 4.92)	
Grether	6	61	3	77
	OR=0.57 (0.22 – 1.46)		OR=1.17 (0.30 – 4.52)	
PROM+Fever	3	15	1	18
	OR=1.36 (0.37 – 5.01)		OR=1.66 (0.20 – 13.70)	

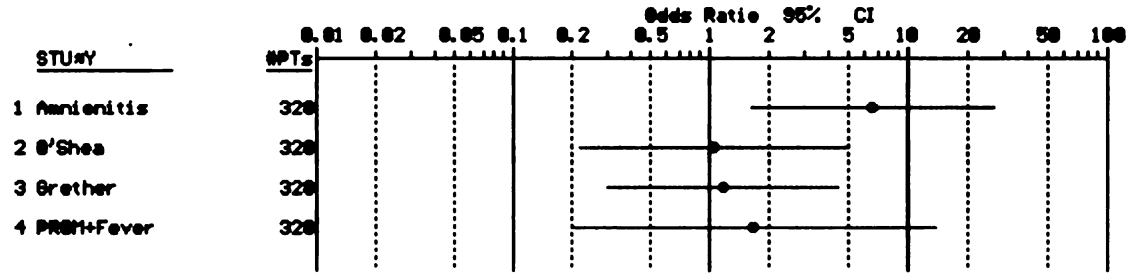
Table 9. Definition of Infection

Amnionitis	O'Shea	Grether	Prom plus Fever
Attendings' diagnosis of chorioamnionitis at discharge	PROM and two: Fever, tenderness, Foul-fluid	Maternal fever greater than 100.4	Maternal Fever>100
Include histologic, microbial, and clinical infection	Antepartum use of antibiotics [42]	Foul smelling discharge	Ruptured membrane
	No UTI	No UTI	No UTI

In graph (below 31 weeks)



In graph (above 31 weeks)



5. Multivariate analysis: Determinants of chorioamnionitis

The Spearman correlation analysis was completed to ascertain the importance of variables that were found to be associated with the chorioamnionitis diagnosis based on the discharge chart. Factors significant statistically ($p<0.05$) in both groups were leukocytosis, maternal fever, maternal tachycardia, and fetal tachycardia. Chorioamnionitis was correlated with PROM only in infants above 31 weeks (Table 10). When logistic regression models included 4 signs, PROM, and demographic factors (sex, race and education) to examine the relative importance of each of these for the definition of chorioamnionitis, the models indicated that demographic factors did not significantly contribute to the models (data not shown). Therefore, models were re-constructed after excluding those three demographic factors. The results (Tables 11 and 12) showed that leukocytosis was important for chorioamnionitis in infants below and above 31 weeks groups (OR=3.56; 95%CI: 1.05-12.08) (OR=3.75; 95%CI: 1.31-10.71). In addition, fetal tachycardia was a significant factor for chorioamnionitis in below 31 weeks group (OR=4.34; 95%CI: 1.23-14.96) while maternal fever and PROM played significant roles

for chorioamnionitis in above 31 weeks group ($OR_{maternal\ fever}$=3.23 95%CI: 1.15-9.12; OR_{PROM}=3.71 95%CI: 1.32-10.37).

Table 10. Univariate Analysis: Spearman correlation coefficients of chorioamnionitis and apparent signs of infection

	Chorioamnionitis (below 31weeks)		Chorioamnionitis (above 31weeks)	
	Spearman r	p-value	Spearman r	p-value
Leukocytosis > 15000	0.17	0.007	0.26	<0.001
Maternal Fever > 37.8 °C	0.15	0.017	0.19	0.001
Maternal Tachycardia > 100	0.20	0.002	0.16	0.005
Fetal Tachycardia > 160	0.21	0.001	0.19	0.001
PROM	0.01	0.86	0.19	<0.001

Table 11. Model #1 Chorioamnionitis and its predictors (below 31 weeks)

Variable	Regression Coefficient	Standard Error	OR	95% CI
Intercept	-5.00	0.85	-	-
Leukocytosis > 15000				
Yes	1.27	0.62	**3.56**	1.05-12.08
No	-	-		
Maternal Fever > 37.8 °C				
Yes	0.70	0.66	2.02	0.56-7.29
No	-	-		
Maternal Tachycardia > 100				
Yes	1.56	0.82	4.77	0.96-23.74
No	-	-		
Fetal Tachycardia > 160				
Yes	1.47	0.63	**4.34**	1.26-14.96
No	-	-		
PROM				
Yes	-0.41	0.77	0.66	0.15-2.99
No	-	-		

Table 12. Model #2 Chorioamnionitis and its predictors (above 31 weeks)

Variable	Regression Coefficient	Standard Error	OR	95% CI
Intercept	-4.69	0.58	-	-
Leukocytosis > 15000				
Yes	1.32	0.54	**3.75**	1.31-10.71
No	-	-		
Maternal Fever > 37.8 °C				
Yes	1.17	0.53	**3.23**	1.15-9.12
No	-	-		
Maternal Tachycardia > 100				
Yes	0.55	0.57	1.74	0.56-5.34
No	-	-		
Fetal Tachycardia > 160				
Yes	1.04	0.59	2.82	0.90-8.90
No	-	-		
PROM				
Yes	1.31	0.53	**3.70**	1.32-10.37
No	-	-		

6. Multivariate Analysis: Predictors of Disabling CP

Multiple logistic regression analysis was performed to examine the association of CP and chorioamnionitis stratified by gestational week 31 less or 31 and above. DCP was the dependent variable. Chorioamnionitis recorded at discharge on the medical chart was the exposure variable of main interest. The covariates were selected based on the knowledge of biological plausibility or the results from the univariate analysis. The covariates included in the models were race, abruptio placenta, route of delivery, SGA, and preterm labor.

Adjusted for the covariates mentioned above, in below 31 weeks group, DCP was not significantly associated with chorioamnionitis (OR=3.53, 95%CI: 0.63-19.68). Abruptio placenta was significantly associated with DCP in this group (OR=4.24 95%CI: 1.34-13.47). In above 31 weeks group, a strong association was demonstrated between chorioamnionitis and DCP after controlling for race, abruptio, route of delivery, SGA, and preterm labor (OR=17.04; 95%CI: 2.75-105.50)

(Table 13 and 14).

Table 13. Model #3 Predictors of DCP (below 31 weeks)

Variable	Regression Coefficient	Standard Error	OR	95% CI
Intercept	-3.29	0.75	-	-
Chorioamnionitis				
Yes	1.26	0.88	3.52	0.63-19.68
No	-	-		
Race				
White	1.13	0.66	3.08	0.85-11.19
Black	-	-		
Abruptio				
Yes	1.44	0.59	**4.24**	1.34-13.47
No	-	-		
Route				
C-section	0.32	0.51	1.38	0.51-3.78
Vaginal	-	-		
SGA				
Yes	-0.57	1.12	0.56	0.06-5.07
No	-	-		
Preterm Labor				
Yes	-0.05	0.51	0.95	0.35-2.58
No				

Table 14. Model #4 Predictors of DCP (above 31weeks)

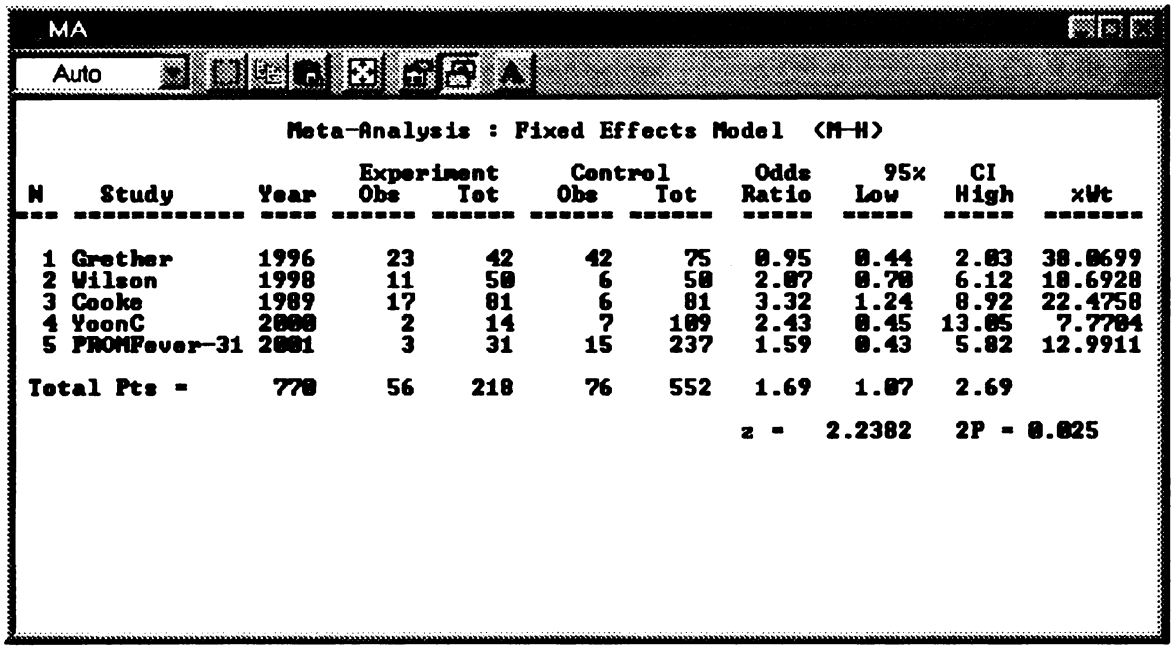
Variable	Regression Coefficient	Standard Error	OR	95% CI
Intercept	-4.70	1.19	-	-
Chorioamnionitis				
Yes	2.84	0.93	**17.04**	2.75-105.50
No	-	-		
Race				
White	-0.24	0.88	0.78	0.14-4.42
Black	-	-		
Abruptio				
Yes	1.51	0.97	4.51	0.68-30.10
No	-	-		
Route				
C-section	0.33	0.80	1.39	0.29-6.65
Vaginal	-	-		
SGA				
Yes	0.92	0.86	2.51	0.47-13.52
No	-	-		
Preterm Labor				
Yes	0.09	0.82	1.10	0.22-5.47
No				

META-ANALYSIS with NBH data added

Finally, an attempt was made to compare the result of the meta-analysis after NBH data was incorporated.

1) Studies dealing with clinical chorioamnionitis plus NBH data-below 31 weeks group

Results from Random Effects Model: Pooled OR = 1.70 (95% CI: 1.04-2.78). The Q statistic showed that the pooled analysis was homogeneous (Q=4.31, P>0.25). Results from the Fixed Effects Model are shown below: Pooled OR = 1.69 (95% CI: 1.07 – 2.69). Chi-square test showed the pooled analysis was homogeneous (X^2 =4.34, p>0.25). A weak positive association was again found from the pooled analysis.



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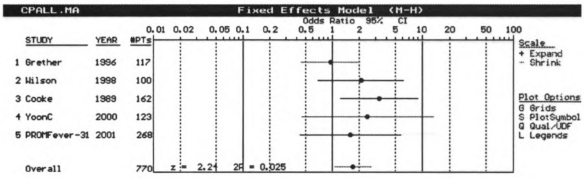
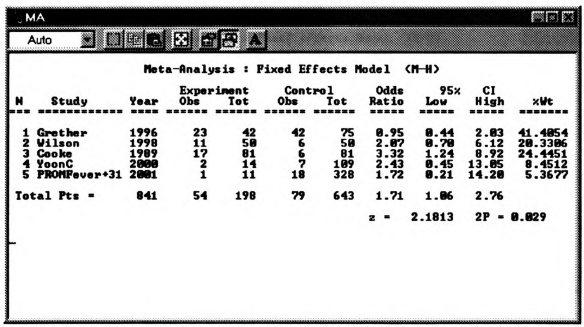


2) Studies dealing with clinical chorioamnionitis plus NBH data-above 31 weeks group

Results from Random Effects Model: Pooled OR = 1.72 (95% CI: 1.03-2.88). The Q statistic showed that the pooled analysis was homogeneous (Q=4.30, P>0.25). Results from the Fixed Effects Model was presented below: Pooled OR = 1.71 (95% CI: 1.06 – 2.76). Chi-square test showed the pooled analysis was homogeneous (X^2 =4.35, p>0.25). A weak positive association was found from the pooled analysis.



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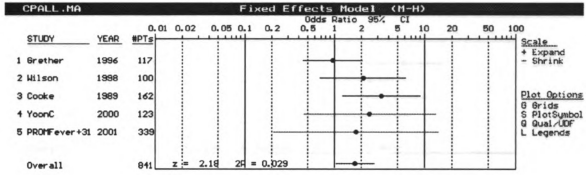
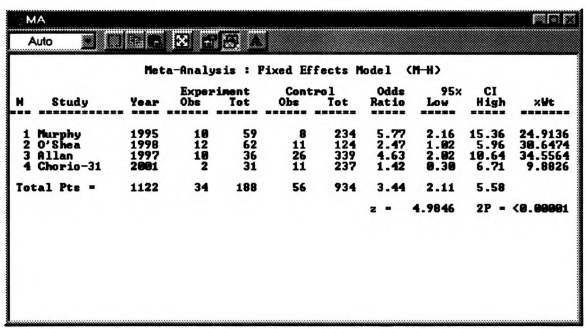


3) Studies dealing with combined chorioamnionitis and NBH data based on discharge diagnosis in hospital charts-below 31 weeks group

Results from Random Effects Model: Pooled OR = 3.56 (95% CI: 2.12-5.99). The Q statistic showed that the pooled analysis was homogeneous (Q=3.33, P>0.25). Results from the Fixed Effects Model are shown below: Pooled OR = 3.44 (95% CI: 2.11 – 5.58). A positive association between CP and chorioamnionitis was found.



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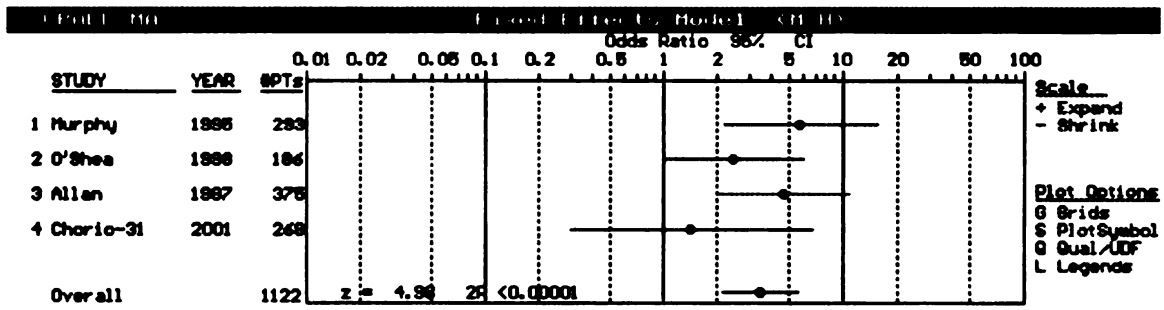
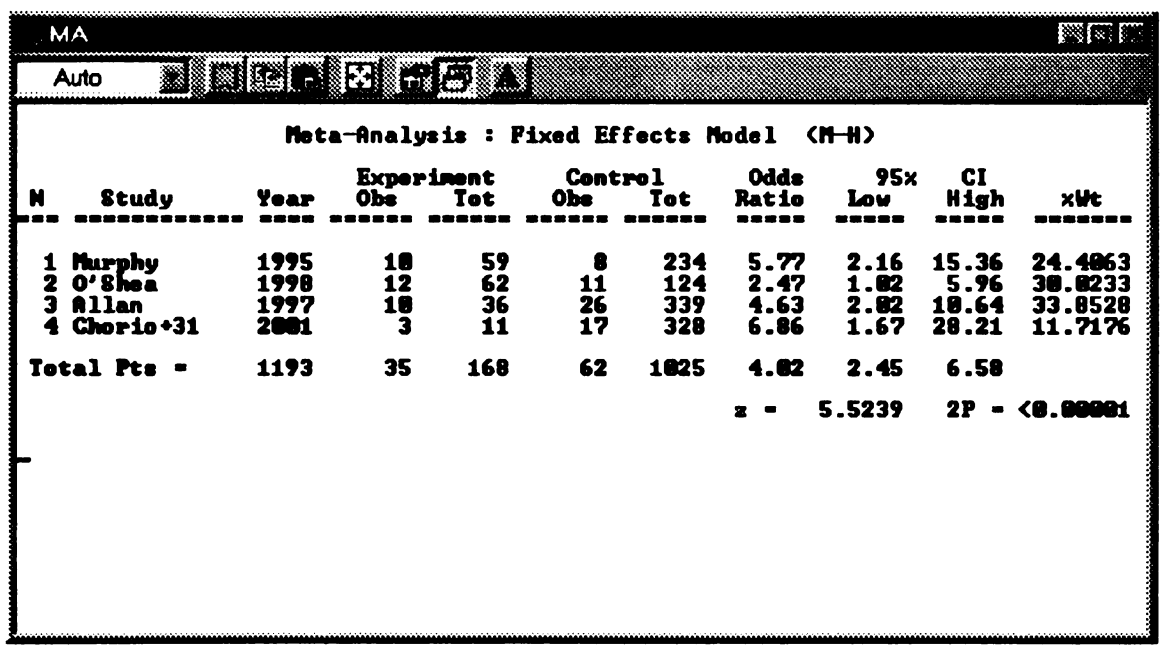


4) Studies dealing with combined chorioamnionitis and NBH data based on discharge diagnosis in hospital charts -above 31 weeks group

Results from Random Effects Model: Pooled OR = 4.23 (95% CI: 4.23-6.87). The Q statistic showed that the pooled analysis was homogeneous (Q=2.31, P>0.25). Results from the Fixed Effects Model presented below: Pooled OR = 4.02 (95% CI: 2.45 – 6.58). In contrast to the other group, a strong positive association between CP and chorioamnionitis was found.


MA

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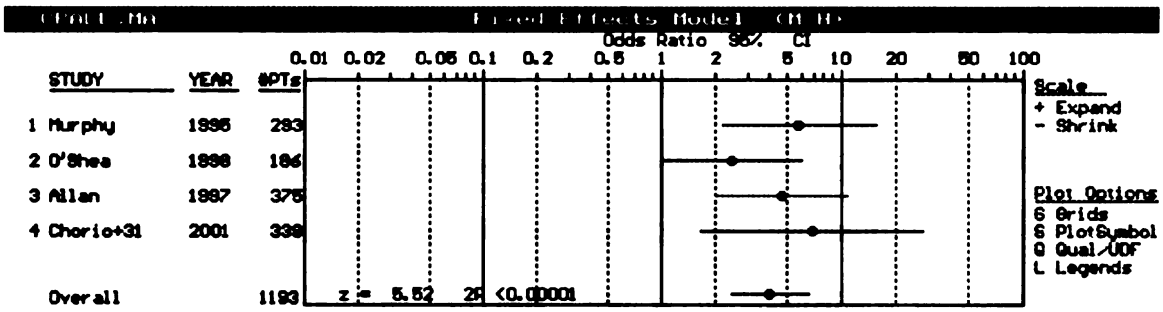
Meta-Analysis : Fixed Effects Model (M-H)

N	Study	Year	Experiment Obs	Experiment Tot	Control Obs	Control Tot	Odds Ratio	95% CI Low	95% CI High	xWt
1	Murphy	1995	18	59	8	234	5.77	2.16	15.36	24.4863
2	O'Shea	1998	12	62	11	124	2.47	1.02	5.96	38.0233
3	Allan	1997	18	36	26	339	4.63	2.02	10.64	33.8528
4	Chorio+31	2001	3	11	17	328	6.86	1.67	28.21	11.7176
Total Pts =		1193	35	168	62	1025	4.02	2.45	6.58	
							z =	5.5239	2P =	<0.00001

In graph:


Odds Ratio 95% CI
0.01 0.02 0.05 0.1 0.2 0.5 1 2 5 10 20 50 100
STUDY YEAR #PTs
1 Murphy 1995 283
2 O'Shea 1998 186
3 Allan 1997 375
4 Chorio+31 2001 339
Overall 1183
z = 5.52
Scale
+ Expand
- Shrink
Plot Options
G Grids
S PlotSymbol
Q Qual/UOF
L Legends

Discussion

The result of this meta-analysis showed that the test of heterogeneity was statistically significant ($Q=11.54$, $p<0.025$) when all 7 selected studies were used. Therefore, the 7 selected studies were stratified into two groups: group1- clinical chorioamnionitis and group II-'combined chorioamnionitis'. The 'combined chorioamnionitis' group represented all other chorioamnionitis except clinical chorioamnionitis, which belonged to group I. The definition of chorioamnionitis in studies of group II was based on the clinician's impression, discharge diagnosis by a clinician, histologic chorioamnionitis, or microbial chorioamnionitis, referred to as combined chorioamnionitis.

The Q-statistics for the test of heterogeneity in both groups indicated that selected studies were homogeneous ($Q_{group\ 1}=4.3$, $p>0.25$; $Q_{group\ 2}=3.33$; $p>0,25$). Clinical chorioamnionitis showed a weak association with DCP (OR=1.71, 95%CI 1.05-2.79), whereas the combined chorioamnionitis demonstrated stronger association with CP (OR=3.83, 95%CI 2.27-6.45).

Another meta-analysis in a recent article showed a significant association between chorioamnionitis and CP [31]. Wu et al showed that clinical chorioamnionitis had a positive association with CP ($OR_{clinical\ chorioamnionitis}=1.9$ (95%CI: 1.4 - 2.5)) in preterm neonates. Among the 11 studies Wu used to analyze the association of clinical chorioamnionitis and CP, some studies did not have a clear definition of clinical chorioamnionitis [43]; Gray's study actually combined clinical and histologic chorioamnionitis into a single category of clinical chorioamnionitis [44]. Misclassification could have existed when the author tried to address the effect of clinical

chorioamnionitis on CP, and yet she included articles defining chorioamnionitis based on both clinical signs and histologic evidence.

The association between clinical chorioamnionitis and CP was not statistically significant (OR=1.6; 95%CI: 0.9 – 2.7) in Wu's meta-analysis. When Wu tried to evaluate the association between the combined chorioamnionitis (clinical or histologic) and CP, a positive association was found (OR = 1.8; 95%CI: 1.5 –2.3)[31]. However, the p-value for the test of homogeneity was 0.07 (If $p<0.10$ the studies are considered heterogeneous and variability in study results is more likely not due to chance alone).

In the NBH data, 31 weeks was used for the categorization of cohorts by GA. Unlike studies done on the basis of birth weight of 1500g, each cohort is homogeneous for analysis because the maturity of organ system is a function of duration of pregnancy and not of weight. Another reason favoring our approach is that 90 percentile of weight for GA 30 weeks intersects 2000g. Therefore, the below 31 weeks group would capture more than 90% of infants less than 31 weeks [19]. Thus below 31 weeks group would sample fewer older neonates with IUGR.

In the NBH data, as seen in meta-analysis, discharge diagnosis of chorioamnionitis showed a stronger association with CP than did three other definitions of chorioamnionitis. As mentioned before, discharge diagnosis of amnionitis in NBH data could represent the combined chorioamnionitis in the meta-analysis. Thus it showed a stronger association with DCP than did the other three definitions in both cohorts (discharge diagnosis of chorioamnionitis will be called as chorioamnionitis in the following discussion).

Among infants below 31 weeks, 13 (5%) of 237 infants had chorioamnionitis. Two of the 13 had DCP, and so the infection did not have a significant association with DCP (OR=1.22, 95% CI 0.26-5.80). After controlling for race, abruptio, route, SGA, and preterm labor, chorioamnionitis showed a slightly stronger association with CP (OR=3.52, 95%CI 0.63-19.68) in this group, but this was not significant. This finding showed that infection is not an important risk factor for DCP in this age group. Chorioamnionitis appeared to be a weaker risk factor in this group. An important risk factor in this cohort was abruptio placenta (OR=4.17 95%CI 1.66-10.44), and there was a significant association between abruptio placenta and CP. The association between CP and abruptio placenta persisted even after controlling for infection, race, route of delivery, SGA, and preterm labor in infants below 31 weeks (OR=4.24, 95% CI 1.34-13.47).

Basic science research and clinical studies indicate a strong association among chorioamnionitis, brain white matter damage (WMD) and CP. Gravett et al produced intraamniotic infection with Group B streptococcus in rhesus monkeys in1994. They showed a sequential and predictable increase of cytokines in amniotic fluid [45]. Introduction of bacteria into newborn kittens was followed by a cytokine cascade and brain white matter damage [46]. Yoon showed white matter damage in rabbits by creating intraamniotic infection in 1997 [47]. Clinical studies, as seen in this meta-analysis, indicated a significant association between chorioamnionitis and CP. Chorioamnionitis appears in some studies to be potentially one of the most important contributors to the development of DCP [15, 48]. The NBH study did not show the association, but this might be from the fact that infants with chorioamnionitis died before

they reached two years of age. There were 113 infants below 31 weeks who died and were singletons. Seven infants among them had chorioamnionitis diagnosed. In order to measure the possible effect of chorioamnionitis on brain damage, PEL/VE was measured as an outcome variable. 21 of 113 dead infants had PEL/VE. Thus another analysis was conducted to measure the combined effect of chorioamnionitis among dead and live infants below 31 weeks. When the outcome variable was defined as PEL/VE in died infants or DCP in live infants, the summary OR showed the following result. The association was still not statistically significant (OR=1.89, 95% CI 0.62-5.73).

Meta-Analysis : Random Effects Model (D&L)

N	Study	Year	Experiment Obs	Experiment Tot	Control Obs	Control Tot	Odds Ratio	95% CI Low	95% CI High	%wt
1	alive	2001	2	31	11	206	1.22	0.26	5.80	50.8747
2	died	2001	3	21	4	75	2.96	0.61	14.42	49.1253
Total Pts =		333	5	52	15	281	1.89	0.62	5.73	

z = 1.1213 2P = 0.26

Overall Heterogeneity: Q = 0.61 Tau^2 = 0.0000

Several studies have reported the importance of subclinical infection in the research of chorioamnionitis. Abruptio placenta has shown a significant association with placental chorioamnionitis in some studies [49]. Clinical decision about the presence of infection was based on clinical signs and symptoms alone as in some studies, particularly when histological findings of placenta were not available. However, studies of infection in rhesus monkeys showed that none of the monkeys with full-blown intraamniotic infection

showed the signs of infection such as fever or leukocytosis [45]. Only 25% of patients who had histologic chorioamnionitis at delivery presented with clinical signs of infection [50]. Bacteria have been recorded at transabdominal amniocentesis from 16.1 percent (0-47.8%) of women in preterm labor with intact membranes [51-53]. When polymerase chain reaction (PCR) was employed to detect bacteria in amniotic fluid in women with preterm labor with intact membranes, a total 55.5 percent of samples were positive, whereas 9.5% of amniotic fluid culture results were positive [54]. These indicate the possibility that many infants with chorioamnionitis have subclinical chorioamnionitis, and do not develop clinical signs of infection. This subclinical infection may be one of the reasons that chorioamnionitis among infants below 31 weeks showed no association with CP. Infants in this age group might have more cases of subclinical chorioamnionitis than older infants. It has been speculated that subclinical chorioamnionitis have contributed to the development of abruptio placenta. Therefore, abruptio placenta with subclinical chorioamnionitis showed a significant association with CP in infants below 31 weeks.

The research above helps to explain the reason why the number of cases exposed to clinical chorioamnionitis ranged widely when different definition of Grether, O'Shea, or PROM plus fever, was used to ascertain the exposure of infection in the NBH data. It appears that there is a need to have a strict definition of chorioamnionitis, which would reflect the real effect of infection on the risk of CP.

In infants above 31 weeks, 20 (6%) of 328 infants had chorioamnionitis. Eleven infants had DCP and three suffered from chorioamnionitis. Thus chorioamnionitis showed a

strong association with CP (OR=6.61, 95% CI 1.61-27.12), and older infants may have severe infection, compared with that of infants below 31 weeks.

Unlike many studies [14, 37, 48], preeclampsia did not show a significant protective effect for DCP in either subset of infants in the NBH data. Most studies have reported a protective effect of preeclampsia when analysis was done in neonates of 500-1500g weights (OR. 0.3–0.6). When NBH data was analyzed by weights (1500g) rather than weeks (31 weeks), a significant protective effect in neonates of 500-1500 g infants was also noted (OR=0.23, 95% CI 0.07-0.77). The association between CP and preeclampsia may be confounded by IUGR because many are growth retarded and of higher gestational age. This confounding effect of IUGR and older gestational ages was not apparent in the NBH analysis when neonates were grouped by gestational age.

Intrauterine growth retardation has been shown to be a risk factor for CP in term or near term infants [55]. This study, however, showed that SGA was not a significant risk factor for CP (OR=0.35, 95%CI 0.04-2.70) in infants below 31 weeks. Incidence of PEL/VE was higher in below 31 weeks group (14 %) than in above 31weeks group (3%).

Finally, this NBH research showed two possible clinical implications. In infants below 31 weeks, the relative contribution of prematurity to the risk of CP outweighs the risk of chorioamnionitis. Some infection in this age group is speculated to be subclinical and mild. Thus, as long as there are no signs of abruptio placenta, all efforts at prolonging gestation would seem warranted by using generous use of broad-spectrum antibiotics. However, in infants above 31 weeks, the contribution of chorioamnionitis to CP is more significant because infection here seems to be severe and symptomatic.

Prompt delivery would be a reasonable choice if there were any signs of infection, or when lung maturity is obtained.

Future research direction:

In order to address the relationship between chorioamnionitis and cerebral palsy more effectively, we need to have a consensus of definition in exposure (chorioamnionitis) and outcome (cerebral palsy). A wide range of false positives and false negatives may exist if subjective symptoms such as uterine tenderness and foul discharge are used to define the exposure.

Therefore, future studies of this relationship should focus on objective and repeatable findings from histology reports, microbial findings of chorioamnionitis, or diagnosis based on objective signs of infection such as leukocytosis, fever, tachycardia and PROM. Blinded observers are recommended when evaluating the presence of clinical chorioamnionitis. The status of CP should be defined for the study. It is highly recommended that prospective studies be conducted with the involvement of multi-centers and multi-discipline experts.

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