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Original article

Maternal chorioamnionitis & long term neurological morbidity in the offspring

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ABSTRACT

Background: Chorioamnionitis is a common and potentially devastating complication of pregnancy associated with maternal and perinatal adverse outcomes.
Objective: To evaluate a possible association between maternal chorioamnionitis and long-term pediatric neurological morbidity.
Study design: A population-based retrospective cohort analysis was performed comparing the risk of long-term neurological morbidity. Pediatric neurological morbidity evaluated included hospitalizations with neurological morbidity. Kaplan–Meier survival curves were constructed to compare the cumulative neurological morbidity and a Cox regression model was used to control for confounders.
Results: 238 622 newborns were included. Of them, 0.5% were born to mothers with chorioamnionitis. 3.1% offspring were hospitalized with a neurological condition. Total neurological morbidity was not significantly more common in the chorioamnionitis group (3.8% vs. 3.1% respectively, OR 1.23, 95% CI 0.9–1.6, $p = 0.147$). However, a significant and independent association was noted between maternal chorioamnionitis and cerebral palsy. (0.5% vs. 0.1%, OR 5.77, 95% CI 2.5–13.0, $p = 0.001$). In a Cox proportional hazards model, controlling for preterm delivery, birthweight, maternal factors and mode of delivery the association between chorioamnionitis and cerebral palsy remained significant (adjusted HR = 2.78, 95% CI 1.20–6.43, P = 0.016).
Conclusion: Maternal chorioamnionitis is associated with cerebral palsy in the offspring, independently of other birth circumstances such as preterm delivery and birthweight.

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1. Introduction

Chorioamnionitis refers to an inflammatory response affecting the membranes and chorion of the placenta.[1] Often diagnosed clinically, this condition is characterized by fever, maternal or fetal tachycardia, uterine tenderness, and foul smelling amniotic fluid. Chorioamnionitis occurs in three to five percent of term births with increased incidence inversely related to gestational age.[2] Multiple studies have indicated that chorioamnionitis can be detected in as many as twenty-five to forty percent of preterm births.[3,4] Chorioamnionitis may also be diagnosed histologically by detecting neutrophil infiltration in amniotic membranes, umbilical cord, or amniotic plate.[5]

Multiple risk factors are associated with chorioamnionitis and diagnostic criteria vary. Recently, the National Institute of Child Health and Human Development Workshop expert panel recommended use of the term "triple I" to try and address the heterogeneity of this diagnosis. The term triple I refers to intrauterine infection or inflammation or both and is defined by strict diagnostic criteria. However, this terminology has not been universally adopted.[6,7] Established risk factors include prolonged labor and/or rupture of membranes, nulliparity, group B streptococcus colonization, bacterial vaginosis, meconium stained fluid, multiple vaginal examinations, epidural anesthesia, drug abuse or smoking, immune compromised states, and more.[7–11]

The long-term effects of chorioamnionitis have long been studied and debated, with studies suggesting increased risk of neonatal morbidity including respiratory distress syndrome, bronchopulmonary dysplasia, early onset sepsis, hypotension, and death.[9] Mounting epidemiological and preclinical evidence implicates prenatal infection and subsequent immune activation in the etiology of schizophrenia.[12] It has been demonstrated that elevated maternal C-reactive protein during pregnancy is associated with an increased risk of schizophrenia in offspring.[12]

Some studies have linked chorioamnionitis to neonatal brain injury and long term neurological damage following infection[13–15] while others have failed to confirm such an association.[16] Although evidence regarding neurological outcome in general is conflicting, an association with cerebral palsy appears plausible.[17,18] The pathophysiology is not fully understood, but evidence demonstrating elevated cytokine levels in neonatal blood and cerebrospinal fluid in children with cerebral palsy further supports the association.[19,20] Increasing evidence suggests that it is low-grade chronic inflammation that leads to neurologic injury rather than acute infection.[21,22]

We sought to evaluate the association between maternal chorioamnionitis and long-term adverse neurological outcomes in the offspring up to 18 years of age, with a specific focus on the risk for cerebral palsy.

2. Materials and methods

A retrospective cohort analysis was performed in order to determine whether children born to mothers diagnosed with chorioamnionitis during the indexed deliveries were at a higher risk for childhood neurological morbidity (up to the age of 18). Chorioamnionitis diagnosis was recorded by obstetrician immediately following delivery following clinical diagnosis by a senior attending obstetrician based on the presence of fever (>38.0 c), maternal (heart rate>100) or fetal (heart rate>160) tachycardia, uterine tenderness, and foul smelling amniotic fluid. The diagnosis is usually based on more than one criterion but not all criteria must be met.

Cerebral palsy diagnosis in general and its subtypes (according to ICD codes listed in the appendix) was recorded by pediatrician specialized in Neurodevelopmental assessment during follow-up in the Child Development Center.

Deliveries occurred during the years of 1991–2013. The study was conducted at the Soroka University Medical Center (SUMC) in Beer-Sheva, Israel. SUMC is the sole hospital in the Negev (southern Israel), thus, the study is based on non-selective population data. The institutional review board (in accordance with the Helsinki declaration) approved the study (#0438-15-SOR approved on March, 2016).

Pregnancies with multiples and fetuses with major congenital malformations were excluded from the analysis. Perinatal deaths (intrauterine fetal death, intra-partum death and post-partum death) were excluded from the long-term analysis. Outcomes assessed included pregnancy characteristics and adverse perinatal outcome, as well as hospitalizations of the offspring up to the age of 18 years involving a predefined set of pediatric neurological morbidities. The different neurological morbidities assessed are detailed in Supplement Table 1. Follow up time was defined as time to an event (first hospitalization with any of the diagnoses listed in the Supplement Table), or until censored. Censoring occurred in case of death (during hospitalization, other than neurologically related) or at age 18 years (which was calculated for each child based on date of birth). Only the first hospitalization for each child was included in the analyses.

Data were collected from two databases that were cross-linked and merged: the computerized hospitalization database of SUMC ("Demog-ICD9"), and the computerized perinatal database of the obstetrics and gynecology department. The Demog-ICD9 database includes demographic information and ICD-9 codes for all medical diagnoses which were made during encounters with SUMC.

The perinatal database consists of information recorded by an obstetrician immediately following delivery. Experienced medical secretaries routinely review the information prior to entering it into the database to ensure its maximal completeness and accuracy. Coding is performed after assessing medical and perinatal records as well as routine hospital documents.

2.1. *Statistical analysis*

Statistical analysis was performed using the SPSS package 23 ed. (SPSS, Chicago, IL). Categorical data was assessed by chi-square for general association. The Student t test was used for differences in continuous variables. Kaplan–Meier survival curves were used to compare neurological morbidity incidences over time for the entire cohort according to maternal

chorioamnionitis status. The differences between the curves was assessed using the log-rank test.

A Cox proportional hazard model was employed which controlled for maternal age at delivery, preterm delivery, birthweight, parity, mode of delivery, maternal diabetes mellitus and any hypertensive disorders. The time scale was defined as time from delivery to event or censoring (i.e. age of 18 years old or end of study period) as the time-dependent variable and Adjusted hazard ratios (aHR) are presented with their 95% confidence intervals (CI). A p value of <0.05 was considered statistically significant.

3. Results

During the study period 238 622 singleton deliveries met the inclusion criteria. Of them, 0.5% (n = 1303) were born to mothers with chorioamnionitis and the remaining 99.5% (n = 237 319) were born to mothers without chorioamnionitis. Pregnancies complicated with chorioamnionitis were 32.72 more likely to end with perinatal mortality (0.5% in the comparison group vs. 13.4% in the exposed group, p < 0.001). Maternal characteristics and immediate pregnancy outcomes, according to the groups, are presented in Table 1.

Long-term neurological morbidity, as evidenced by hospitalizations of the offspring up to 18 years of age is presented (in total and in sub-categories) in Table 2. In the control group median follow up was 10.3 years (range 0–18) and in the chorioamnionitis group it was 12.7 years (range 0–18 years, p < 0.001). Total pediatric neurological morbidity was comparable between the groups (3.8% vs. 3.1%, OR 1.23, 95% CI 0.93–1.64, $p = 0.147$). However, an association was found between maternal chorioamnionitis and increased risk for hospitalizations involving a diagnosis of cerebral palsy (0.5% vs. 0.1%, OR 5.77, 95% CI 2.5–13.0, $p = 0.001$).

Kaplan–Meier survival curves were constructed to demonstrate the long-term cumulative incidence of total neurological hospitalizations, and chorioamnionitis group did not exhibit a significantly higher cumulative incidence of total neurological hospitalizations (Log rank $p = 0.323$), however, a higher cumulative incidence of cerebral palsy related hospitalizations was noted (Log rank $p < 0.001$) (see Figs. 1 and 2).

Table 3 present the adjusted hazard ratio for cerebral palsy, in offspring of mothers with chorioamnionitis, as evaluated in a Cox proportional hazards model. The model adjusted for maternal age and parity, birthweight, preterm delivery, mode of delivery, maternal diabetes and maternal hypertensive disorders during pregnancy. The model confirmed the independent association between chorioamnionitis and cerebral palsy with an adjusted hazard ratio of 2.78 (95%CI 1.20–6.43, $p = 0.016$). An independent association between maternal chorioamnionitis and general neurological morbidity in the offspring, however, was not established with an adjusted hazard ratio of 0.91 (95% CI 0.69–1.21, $p = 0.53$).

4. Discussion

In this large cohort of children followed up to 18 years of age, a significant and independent association between maternal chorioamnionitis and the risk for cerebral palsy in the offspring was noted with an adjusted hazard ratio of 2.786. In our analyses, we have adjusted for important obstetrical confounders such as preterm delivery and birthweight and by doing so were able to control the major confounding effect of prematurity, strongly associated with chorioamnionitis.

Chorioamnionitis is a common and potentially devastating complication of pregnancy associated with significant maternal, perinatal, and long-term adverse outcomes. Maternal complications range from a simple postpartum infection, which may respond to antibiotic treatment, to full-blown sepsis. Rarely, chorioamnionitis may lead to maternal death. For the newborn, complications are divided to short and long-term. Clearly, chorioamnionitis increases the risk for neonatal

Table 1 – Maternal characteristics and pregnancy outcomes, chorioamnionitis group vs. comparison group.

		Chorioamnionitis n = 1303	Comparison group n = 237 319	Odds Ratio	95% CI	p value
Maternal age (years)		29.1 ± 6.2	28.15 ± 5.8	–	−1.268–0.633	<0.001
Gestational age at birth (weeks, mean ± SD)		36.66 ± 4.0	39.17 ± 1.7	–	2.413–2.602	<0.001
Parity (%)	1–4	75	75.6	0.971	0.85–1.10	0.645
	5+	25	24.4			
Maternal diabetes (gestational and pre-gestational, %)		8.8	5.0	1.832	1.51–2.22	<0.001
Maternal hypertension (chronic, gestational, and preeclampsia, %)		8.5	5.0	1.758	1.44–2.13	<0.001
Preterm delivery (<34 weeks) %		22.3	0.9	31.83	27.75–36.52	<0.001
Preterm delivery (<37 weeks) %		41	6.3	10.40	9.30–11.63	<0.001
Cesarean delivery %		52.8	13.5	7.18	6.44–8.01	<0.001
Low 1 min Apgar score (<7) %		21.9	3.3	8.14	7.12–9.30	<0.001
Low 5 min Apgar score (<7) %		2.0	0.3	6.72	4.53–9.98	<0.001
Small for gestational age		7.8	4.5	1.79	1.46–2.20	<0.001
Median follow up (years, median, range)		12.7 (0–18)	10.3 (0–18)	–	–	<0.001

Table 2 – Incidence of neurological hospitalizations of the offspring in both groups.

Neurological Hospitalization	Chorioamnionitis group	Control group	Odds Ratio	95% Confidence Interval	*p* value
Total	3.8% (50)	3.1% (7416)	1.23	0.93–1.64	0.147
CP	0.5% (6)	0.1% (190)	5.77	2.55–13.0	0.001
PDD	0% (0)	<0.001 (28)	0.99	0.99–0.99	0.695
Eating disorders	0.2% (3)	0.2% (431)	1.27	0.4–3.9	0.515
Sleep disorders	0% (0)	<0.1% (46)	0.99	0.99–0.99	0.615
Movement disorders	1.8% (24)	1.9% (4407)	0.99	0.66–1.48	0.98
Developmental disorders	0.2% (2)	0.1% (233)	1.56	0.38–6.29	0.36
Psychiatric- Emotional	0.7% (9)	0.5% (1171)	1.4	0.72–2.71	0.315
ADHD	0.1% (1)	0.1% (141)	1.29	0.18–9.24	0.541
Myopathy	0.1% (1)	0.1% (135)	1.34	0.19–9.65	0.52
Headache	0% (0)	<0.1% (53)	0.99	0.99–0.99	1
Degenerative, Demyelination	0% (0)	0.1% (179)	0.99	0.99–0.99	1
Other	0.5% (5)	0.5% (904)	1.0	0.41–2.43	0.82

CP – Cerebral Palsy.
PDD – Pervasive Developmental Disorders.
ADHD – Attention Deficit Hyperactivity Disorder.

infection, which may deteriorate into sepsis and death before or after delivery. In the long term, associated complications may include chronic lung disease and brain injury leading to cerebral palsy and other neurodevelopmental disabilities.[13–15] However, it is always challenging to separate complications resulting from the associated prematurity to those resulting independently from the maternal intrauterine infection itself. Prematurity, strongly associated with chorioamnionitis, may be the result of preterm labor due to the inflammatory state directly, or induced by the medical team due to maternal status severity.

Prematurity has a dramatic impact on long-term offspring health, with neurodevelopmental handicap being a major concern. Studies have shown that preterm infants born to mothers with chorioamnionitis are at risk for adverse neurodevelopmental outcome.[5,23,24] Several authors have observed an increased risk of severe intraventricular hemorrhage (IVH) and/or periventricular leukomalacia (PVL)[25–30] in preterm infants exposed to chorioamnionitis. A large meta-analysis showed that clinical chorioamnionitis was significantly associated with the development of cystic periventricular leukomalacia and cerebral palsy (CP), but histological

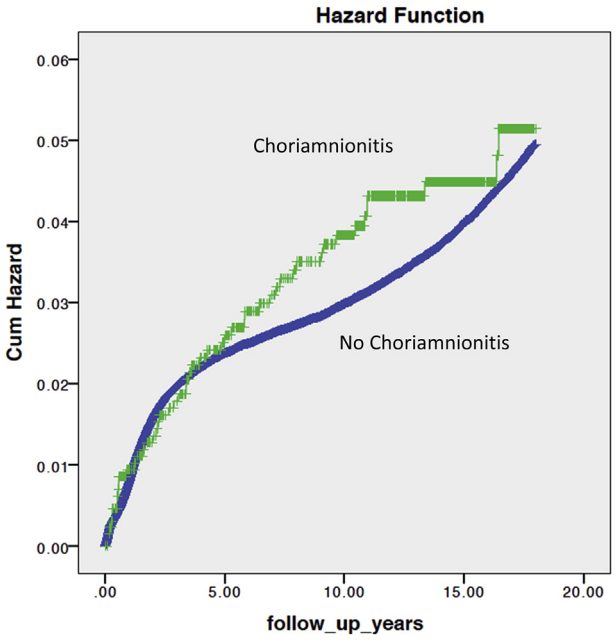

Fig. 1 – Kaplan meier survival curve – Total cumulative hazard for neurological related hospitalizations in the choriamnionitis group vs. the control group. Log rank p value = 0.323.

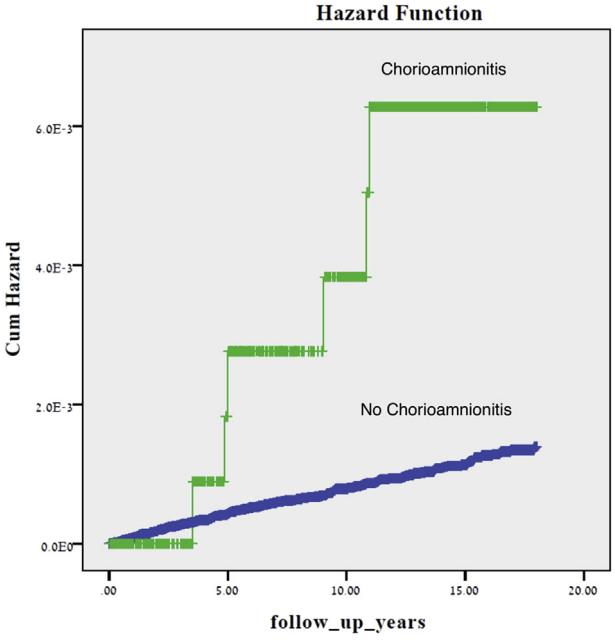

Fig. 2 – Kaplan meier survival curve – Total cumulative hazard for cerebral palsy (CP) related hospitalizations in the choriamnionitis group vs. the control group. Log rank p value < 0.001.

Table 3 – The risk for long-term pediatric cerebral palsy hospitalizations; a Cox proportional hazards model.

	Adjusted hazard ratio	95% CI	*p* value
Chorioamnionitis	2.78	1.20–6.43	0.016
Maternal age	0.98	0.96–1.0	0.372
Preterm delivery	2.79	1.91–4.08	<0.001
Maternal diabetes (gestational and pre-gestational)	0.73	0.37–1.46	0.381
Maternal hypertension (chronic, gestational, and preeclampsia)	1.06	0.61–1.85	0.830
Cesarean section	1.69	1.18–2.42	0.004

chorioamnionitis was only associated with development of periventricular leukomalacia in preterm infants.[31]

Cerebral palsy describes a group of disorders in the development of movement and posture, caused by non-progressive disturbances occurring in the developing fetal or infant brain.[32] The mechanism by which maternal chorioamnionitis contributes to cerebral palsy is not well understood. It is well established that infections activate inflammatory pathways, causing the release of various pro-inflammatory biomarkers (cytokines, interleukins, and other molecules).[33,34] Pro-inflammatory cytokines can cause direct damage to oligodendrocytes and neurons via the activation of microglial cells, neurotoxicity, and thus, neurobehavioral abnormalities.[33] The unifying hypothesis is the overwhelming fetal production of cytokines leading to brain cell damage.[33,34]

The association between CP and birthweight has been previously suggested by several authors. A large European study of 4500 children with CP, showed that the likelihood of severe CP was greater at the extremes of birthweight. Babies of 32–42 weeks' gestation with a birthweight below the 10th percentile for gestational age were 4–6 times more likely to have cerebral palsy than were children in a reference band. In children with a weight above the 97th percentile, the increased risk was smaller (from 1.6 to 3.1), yet significant.[35] In our cohort, CP was more common in the maternal chorioamnionitis group while controlling for birthweight thus supporting the independent association between maternal chorioamnionitis and CP.

Diagnosis of Cerebral Palsy is routinely made by a pediatrician specializing in child development. Severe forms of CP are diagnosed earlier in the child's life. However, milder cases may be diagnosed later. Our study is based on hospitalizations only. Thus, even if a child is diagnosed at the age of 2 years, but is not hospitalized, our database will not reflect the age of diagnosis but rather the age of any first hospitalization, in which this (CP) diagnosis exists, as the main or the background diagnosis.

Maternal chorioamnionitis was associated, in our cohort, with maternal diabetes, hypertension, and intra uterine growth restriction (Table 1). This finding can partially be explained by the obvious association with preterm delivery. However, some previously published evidence suggests an independent link to diabetes, and growth restriction.[36,37]

Our study's main strength is the population-based nature of the data, and the fact that our hospital is the only hospital serving the entire population of southern Israel. This hospital provides both maternity services and pediatric services; thus, as long as patients live in the area, they would most likely be diagnosed and treated here. Nevertheless, the possibility that some patients received pediatric neurological care elsewhere, cannot be ruled out. In addition, a few other limitations should be addressed when considering our results. This study was retrospective and by nature has inherent limitation in data ascertainment and misclassification. It should be noted that the diagnosis of Cerebral Palsy is routinely made by a pediatrician specializing in child development. Severe forms of CP are diagnosed earlier in the child's life. However, milder cases may be diagnosed later. Our study is based on hospitalizations only. Thus, even if a child is diagnosed at the age of 2 years, but is not hospitalized, our database will not reflect the age of diagnosis but rather the age of any first hospitalization, in which this (CP) diagnosis exists, as the main or the background diagnosis. Another limitation is that the diagnosis of chorioamnionitis is heterogenic and although based on criteria, variations still exists between physicians that register the diagnosis. In contrast to the well-defined outcome, the exposure was less clearly defined. Our institution holds a protocol for chorioamnionitis diagnosis and management and includes specific definitions, however, the protocol also includes clinical suspicion, which is based solely on the physician's subjective impression. We cannot know which of these criteria were implemented in each exposed case.

We followed newborns up to the age of 18 years (median follow up time 10.1 years). It is possible that a longer follow-up in all individuals may have revealed additional neurological morbidities. This important point remains to be investigated in future epidemiological studies. In addition, it is possible that many of the neurological conditions were diagnosed and treated outside of the hospital and thus would not have been picked up in our database, although this is equally true for both groups. Another limitation of our study is that multiple pregnancies were excluded. It is well known that the prevalence of CP is higher in this population.[38]

It should be noted that the diagnosis chorioamnionitis in our study was made in only 0.5% of cases (lower than expected). We suspect that these low incidences reflect underdiagnosis, specifically of milder cases. Chorioamnionitis that was not full blown during delivery, but only apparent later on or in the pathological examination of the placenta, or during the later postpartum period, would not have been categorized as such. This possible misclassification bias suggests that in our study the exposed group includes severe chorioamnionitis cases while the comparison group probably includes the milder chorioamnionitis cases.

To conclude, chorioamnionitis appears to have a significant association specifically with CP. Maternal infected uterus remains an obstetrical emergency that should be treated as such, and more is to be done within the realms of prevention and treatment of this dangerous condition.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2019.03.005.

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