creative commons
COMMONS DEED

저작자표시-비영리-동일조건변경허락 2.0 대한민국

이용자는 아래의 조건을 따르는 경우에 한하여 자유롭게

- 이 저작물을 복제, 배포, 전송, 전시, 공연 및 방송할 수 있습니다.
- 이차적 저작물을 작성할 수 있습니다.

다음과 같은 조건을 따라야 합니다:

저작자표시. 귀하는 원저작자를 표시하여야 합니다.

비영리. 귀하는 이 저작물을 영리 목적으로 이용할 수 없습니다.

동일조건변경허락. 귀하가 이 저작물을 개작, 변형 또는 가공했을 경우에는, 이 저작물과 동일한 이용허락조건하에서만 배포할 수 있습니다.

- 귀하는, 이 저작물의 재이용이나 배포의 경우, 이 저작물에 적용된 이용허락조건을 명확하게 나타내어야 합니다.
- 저작권자로부터 별도의 허가를 받으면 이러한 조건들은 적용되지 않습니다.

저작권법에 따른 이용자의 권리는 위의 내용에 의하여 영향을 받지 않습니다.

이것은 이용허락규약(Legal Code)을 이해하기 쉽게 요약한 것입니다.

Disclaimer

dCollection

의학석사 학위논문

극소 저체중 출생아에서 다양한 기준으로 진단한 융모양막염의 유무에 따른 신생아 유병률의 비교

2015 년 2 월

서울대학교 대학원

임상의과학과

김 수 영

극소 저체중 출생아에서 다양한 기준으로 진단한 융모양막염의 유무에 따른 신생아 유병률의 비교

A Comparison of the Incidence of Neonatal Morbidities Using Various Criteria for Histologic Chorioamnionitis in Very Low Birth Weight Infants

February 2015

The Department of Clinical Medical Sciences,
Seoul National University
College of Medicine
Suyeong Kim

의학석사 학위논문

A Comparison of the Incidence of Neonatal Morbidities Using Various Criteria for Histologic Chorioamnionitis in Very Low Birth Weight Infants

by
Suyeong Kim

A thesis submitted to the Department of Medicine
in partial fulfillment of the requirements for the
Degree of Master of Science in Medical Sciences
at Seoul National University College of Medicine

December 2014

Approved by Thesis Committee:

Professor_____Chairman
Professor_____Vice chairman
Professor_____

극소 저체중 출생아에서 다양한 기준으로 진단한 융모양막염의 유무에 따른 신생아 유병률의 비교

지도교수 최 창 원

이 논문을 의학 석사 학위논문으로 제출함

2014년 10월

서울대학교 대학원

임상의학과

김 수 영

김수영의 석사 학위논문을 인준함

2014년 12월

위 원 장 _____ (인)

부위원장 _____ (인)

위 원 _____ (인)

ABSTRACT

A Comparison of the Incidence of Neonatal Morbidities Using Various Criteria for Histologic Chorioamnionitis in Very Low Birth Weight Infants

Suyeong Kim
Medical Science, Medicine
The Graduate School
Seoul National University

Background: Although there have been many studies supporting the adverse effects of histologic chorioamnionitis (HC) on neonatal outcomes, debates continue on this issue.

Objectives: To determine the relationship between HC and neonatal morbidities in very low birth weight (VLBW) infants using criteria reflecting the extent and site of inflammation.

Methods : We performed a retrospective cohort study of 261 VLBW infants who were admitted to a single tertiary academic center between 2008 and 2012. Based on the site within the placenta and the extent of neutrophil infiltration, four criteria for HC were developed that reflected the severity of the inflammatory process and the site of inflammation. We compared the incidence of neonatal morbidities in VLBW infants with and without HC using different HC criteria.

Results: The gestational age (GA) was significantly lower for the HC-exposed group compared to the unexposed group. The birth weight and sex ratio were not different. The incidence of BPD was higher in the HC-exposed infants based on criterion 2. HC was significantly associated with severe ROP (≥stage 3) and the need for laser surgery, based on criteria 1 and 3. However, the relationship disappeared upon further analysis after adjusting for GA and birth weight. On the other major morbidities, we did not observe an independent relationship with HC either except respiratory distress syndrome (RDS) which showed a decreased incidence among the HC-exposed infants, based on all of the criteria.

Conclusions: The results of this study indicate that HC significantly decreases the risk of RDS but has no associations with other morbidities.

Keywords : chorioamnionitis; histologic chorioamnionitis; neonatal morbidity; very low birth weight; preterm infants

Student Number : 2013-22596

CONTENTS

LIST OF TABLES AND FIGURES

INTRODUCTION

Histologic chorioamnionitis (HC) is characterized by a maternal inflammatory response that involves the neutrophilic infiltration of the membranes or the chorionic plate, with or without a fetal inflammatory response (FIR), which is associated with funisitis [1]. HC is a reliable marker of an ascending genital tract infection, and the inflammation associated with HC is a major risk factor for preterm birth, particularly at an early gestational age (GA), and significantly contributes to prematurity-associated morbidities. There have been not a few studies supporting the adverse effects of HC on neonatal outcomes, but controversies continue on this issue [2-9].

The FIR associated with HC may contribute to adverse neonatal outcomes [10]. Amnionitis is the final stage of extra-placental chorioamnionitic inflammation. Park et al. [11] demonstrated that the involvement of the amnion in the inflammatory process is associated with more intense fetal and intra-amnionitic inflammatory responses compared with chorionitis alone. Yoon et al. [1] reported that funisitis is associated with amniotic fluid infections, congenital neonatal sepsis, and FIR syndrome. In this study, amnionitis or funisitis were mainly considered when defining HC to determine the severity of the inflammatory process and to enable clinicians to determine the likelihood of fetal involvement. A recent meta-analysis of 59 studies reported that the definition of chorioamnionitis varied across the studies [12]. Different studies used different definitions; therefore, the real

effects of HC have been confounded by the absence of both a standardized definition and standardized histologic diagnostic criteria. The aim of this study was to determine the relationship between HC and neonatal morbidities in very low birth weight (VLBW) infants, using various criteria that reflect both the extent and the site of inflammation.

MATERIALS AND METHODS

This is a retrospective study. The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital. Informed consent was waived by the IRB. The study included all survived infants with a birth weight of < 1,500 g who were born and admitted to the intensive care nursery at Seoul National University Bundang Hospital between January 2008 and December 2012. We excluded infants with major congenital anomalies and infants whose placentas were not available for pathologic assessment.

The placentas were routinely sent for histologic examination in our center. HC was diagnosed in the presence of acute inflammation and the infiltration of polymorphonuclear leukocytes (PMN) into the amnion, the chorionic decidua, the umbilical cord or the chorionic plate, and it was described in four grades depending on the extent of the leukocyte infiltration, using the grading system devised by Salafia et al. (Table 1) [13]. Based on the histological findings described using this grading system, HC was classified using 4 criteria, depending on the degree of inflammation noted at each site (Table 2). PMN infiltration with any grade in any part of the amnion, chorionic decidua, umbilical cord or chorionic plate was defined as HC under criterion 1. Amnionitis with PMN infiltration into the amnion was defined as HC under criteria 2. Funisitis with PMN infiltration into the umbilical cord was defined as HC under criteria 3. The presence of both amnionitis and funisitis were defined as HC under criterion 4. The absence and the presence of chorionic

deciduitis and chorionitis were neglected under criteria 2-4. We compared the incidence of neonatal morbidities in VLBW infants with and without HC using the above criteria for HC.

We retrospectively collected antenatal, perinatal and neonatal data from the original medical records of the infants included in this study. The retrieved data included maternal age, type of delivery, antenatal steroid use, premature rupture of membranes (PROM) > 18 hours, antenatal antibiotic use, the clinical diagnosis of chorioamnionitis, a placental pathologic diagnosis, maternal preeclampsia, GA, birth weight, gender, multiple births, small for gestational age (SGA), Apgar scores at 1 and 5 minutes and umbilical blood pH. SGA was defined as a birth weight less than the 10th percentile for gestational age. Neonatal morbidities were compared between the HC-exposed and the HC-unexposed infants. Morbidities included respiratory distress syndrome (RDS), defined by the presence of respiratory distress, as indicated by an increased oxygen requirement (fractional concentration of inspired oxygen ($FiO_2 \geq 0.4$) and compatible chest radiographic findings in the absence of evidence of another cause of respiratory disease; bronchopulmonary dysplasia (BPD), defined as supplemental oxygen dependency at 36 weeks of corrected gestational age; early-onset sepsis and late-onset sepsis, defined as a systemic bacterial infection documented by a positive blood culture within the first 72 hours of life or after the first 72 hours of life, respectively, with a clinical presentation consistent with sepsis; intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL), as

diagnosed via cranial ultrasonography; patent ductus arteriosus, as diagnosed via echocardiography; necrotizing enterocolitis (NEC), as defined according to Bell et al. [14]; and retinopathy of prematurity (ROP), defined based on the International Classification of Retinopathy of Prematurity.

Statistical analyses were performed using SPSS software, Version 21.0 (SPSS, Inc., Chicago, Ill., USA). Continuous variables are expressed as the means and SDs or as medians and interquartile ranges and were analyzed using either Student's t-test or the Mann-Whitney U test. Categorical variables are expressed as proportions (%), and the χ^2 or Fisher's exact tests (two-sided) were used for comparisons. Logistic regression models adjusting for both GA and birth weight were performed. Odds ratios (OR) and 95% confidence intervals (CI) were reported, and a p value <0.05 was considered statistically significant.

Table 1. Grading system for histologic chorioamnionitis (quoted from Salafia et al. [13])

Amnion and chorion-decidua
Grade 1- One focus of at least five PMNs
Grade 2- More than one focus of grade 1 inflammation, or at least one focus of five to 20 PMNs
Grade 3- Multiple and/or confluent foci of grade 2
Grade 4- Diffuse and dense acute inflammation
Umbilical cord
Grade 1- PMNs within the inner third of the umbilical vein wall
Grade 2- PMNs within the inner third of at least two umbilical vessel walls
Grade 3- PMNs in the perivascular Wharton jelly
Grade 4- Panvasculitis and funisitis extending deep into the Wharton jelly
Chorionic plate
Grade 1- One focus of at least five PMNs in subchorionic fibrin
Grade 2- Multiple foci of grade 1 in subchorionic fibrin
Grade 3- Few PMNs in connective tissue or chorionic plate
Grade 4- Numerous PMNs in chorionic plate, and chorionic vasculitis

Abbreviation: PMNs, polymorphonuclear leukocytes

Table 2. The criteria for diagnosing histologic chorioamnionitis based on the site of inflammation

Criteria	Definition
Criterion 1	PMN infiltration with any grade in any part of the amnion, chorionic decidua, umbilical cord or chorionic plate
Criterion 2	PMN infiltration with any grade in the amnion (amnionitis)
Criterion 3	PMN infiltration with any grade in the umbilical cord (funisitis)
Criterion 4	PMN infiltration with any grade in the part of the amnion and umbilical cord (amnionitis+funisitis)

RESULTS

During the study period, 261 VLBW infants were born and admitted to our neonatal intensive care unit, and their eligibility to participate in the study was assessed. Among them, two infants were excluded because of insufficient placental histologic data.

Twenty six infants (10.0%) died before discharge. The mortality rates were not different between HC-exposed and the unexposed infants based on each criterion (8.1% vs 10.7%, p=0.491). Of the remaining 233 infants, 90 infants (38.6%) were exposed to HC. The demographic and perinatal characteristics of the VLBW infants who were exposed and were not exposed to HC based on various criteria are summarized in Table 3. Mothers with HC were more likely to have PROM and clinical chorioamnionitis, receive antibiotics, and deliver vaginally. Mothers without HC were more likely to have preeclampsia. The mean GA was significantly lower among the HC-exposed infants. The HC-exposed infants were more likely to be of singleton gestation and less likely to be SGA. The mean umbilical blood pH was higher among the HC-exposed infants, but the difference was not statistically significant. There were no significant differences in sex, antenatal steroid exposure rates or median Apgar scores at 1 and 5 minutes

We compared the neonatal characteristics and the incidences of neonatal morbidities between the HC-exposed group and the unexposed group, using the criteria for HC (Table 4). The mean GA was significantly lower among the HC-exposed infants based on each of the criteria. The mean birth weight were

not different between the HC-exposed and the unexposed infants based on each criterion. The incidences of RDS, IVH of grade ≥3, PVL, and early-onset and late-onset sepsis were not different between HC-exposed and unexposed infants based on each criterion. The incidence of BPD was higher in the HC-exposed infants based on criterion 2. HC was significantly associated with severe ROP (≥stage 3) and the need for laser surgery, based on criteria 1 and 3. However, this relationship disappeared upon further analysis after adjusting for both GA and birth weight. Only the adjusted ORs for the incidence of RDS were significantly lower among the HC-exposed infants, based on each criterion (Table 5).

Table 3. Demographic and perinatal characteristics of very low birth weight infants exposed to histologic chorioamnionitis as defined by various criteria

	Criterion 1 (n=91)	Criterion 2 (n=18)	Criterion 3 (n=31)	Criterion 4 (n=12)	No-HC (n=142)
Maternal characteristics					
Maternal age† (years)	32.6 ± 3.6	33.7 ± 3.8	32.6 ± 3.5	32.5 ± 3.2	32.7±3.8
Cesarean section (%)	*53 (59.3)	*5 (27.8)	*12 (38.7)	*2 (16.7)	125 (88.0)
Antenatal steroid (%)	80 (87.9)	17 (94.4)	29 (93.5)	11 (91.7)	114 (80.3)
ROM >18 h (%)	*57 (62.6)	*18 (100)	* 27 (87.1)	*12 (100)	21 (14.8)
Intrapartum antibiotics exposure (%)	*49 (53.8)	*15 (83.3)	*23 (74.2)	*9 (75.0)	17 (12.0)
Clinical chorioamnionitis (%)	*6 (6.6)	1 (5.6)	*5 (16.1)	1 (8.3)	0 (0)
Multiple gestations (%)	*19 (20.9)	*0 (0)	*2 (6.5)	*0 (0)	52 (36.6)
Maternal PE (%)	*10 (11.0)	*0 (0)	*1 (3.2)	0 (0)	65 (45.8)
Neonatal characteristics					
GA† (weeks)	$*28^{+3} \pm 2^{+3}$	$*27^{+6} \pm 1^{+6}$	$*28^{+1} \pm 2^{+2}$	$*28^{+1} \pm 1^{+5}$	$30^{+1} \pm 2^{+4}$
Birth weight† (g)	1089 ± 261	1105 ± 260	1080 ± 286	1136 ± 255	1113±275
Males (%)	48 (53.8)	8 (44.4)	13 (41.9)	5 (41.7)	63 (44.4)
SGA (%)	*17 (18.7)	*2 (11.1)	*4 (12.9)	*1 (8.3)	70 (49.3)
Apgar score‡ at 1 min	5 (3, 6)	6 (3.75, 6.25)	5 (4, 6)	6 (5, 6.75)	5 (3, 6)
Apgar score‡	7 (6, 7.25)	7 (6, 8)	7 (6, 7)	7 (6.25, 7.75)	7 (6, 8)

at 5 min

A comparison of demographic and perinatal characteristics of histologic chorioamnionitis with regard to the presence or absence of histologic chorioamnionitis using various criteria

*P value <0.05

†Data expressed as the means ± standard deviations

‡Data expressed as medians (interquartile ranges)

Abbreviation: GA; gestational age; HC, histologic chorioamnionitis; PE, preeclampsia; ROM, rupture of membrane; SGA, small for gestational age

Table 4. A comparison of demographic and clinical characteristics of histologic chorioamnionitis with regard to the presence or absence of histologic chorioamnionitis using various criteria

	The presence of HC versus the absence of HC defined by							
	Criterion 1		Criterion 2		Criterion 3		Criterion 4	
	Y (n=91)	N (n=142)	Y (n=18)	N (n=215)	Y (n=31)	N (n=202)	Y (n=12)	N (n=221)
GA	*$28^{+3}\pm2^{+3}$	$30^{+1}\pm2^{+4}$	*$27^{+6}\pm1^{+6}$	$29^{+5}\pm2^{+5}$	*$28^{+1}\pm2^{+2}$	$29^{+5}\pm2^{+5}$	*$28^{+1}\pm1^{+5}$	$29^{+4}\pm2^{+5}$
Bwt	1089±261	1113±275	1105±260	1103±271	1080±286	1107±268	1136±255	1101±271
RDS (%)	49 (53.8)	74 (52.1)	7 (38.9)	116 (54.0)	14 (45.2)	109 (54.0)	4 (33.3)	119 (53.8)
BPD (%)	27 (29.7)	32 (22.5)	*9 (50.0)	50 (23.3)	9 (29.0)	50 (24.8)	4 (33.3)	55 (24.9)
NEC (%)	5 (5.5)	8 (5.6)	1 (5.6)	12 (5.6)	3 (9.7)	10 (5.0)	1 (8.3)	12 (5.4)
IVH ≥ Gr 3 (%)	7 (7.7)	5 (3.5)	0 (0)	12 (5.6)	3 (9.7)	9 (4.5)	0 (0)	12 (5.4)
PVL (%)	5 (5.5)	12 (8.5)	0 (0)	17 (7.9)	3 (9.7)	14 (6.9)	0 (0)	17 (7.7)
Early sepsis (%)	1 (1.1)	0 (0)	0 (0)	1 (0.5)	0 (0)	1 (0.5)	0 (0)	1 (0.5)
Late sepsis (%)	7 (7.7)	13 (9.2)	3 (16.7)	17 (7.9)	1 (3.2)	19 (9.4)	1 (8.3)	19 (8.6)
Severe ROP	*26 (28.6)	24 (16.9)	6 (33.3)	44 (20.5)	*11 (35.5)	39 (19.3)	3 (25.0)	47 (21.3)

(%)								
Laser op (%)	*23 (25.3)	16 (11.3)	5 (27.8)	34 (15.8)	* 9 (29.0)	30 (14.9)	3 (25.0)	36 (16.3)

**P* value <0.05

Abbreviation: BPD, bronchopulmonary dysplasia; Bwt, birth weight; GA; gestational age; Gr, grade; HC, histologic chorioamnionitis; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; op, operation; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity

Table 5. Odds ratios and 95% confidence intervals of the relationship between neonatal morbidities and histologic chorioamnionitis as defined by various criteria

	The presence of HC versus the absence of HC defined by							
	Criterion 1		Criteria 2		Criteria 3		Criteria 4	
	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI
RDS	*0.402	0.191-0.847	*0.192	0.05-0.742	*0.25	0.088-0.706	*0.188	0.038-0.927
BPD	0.851	0.399-1.817	0.691	0.255-1.87	0.691	0.255-1.87	1.1	0.253-4.778
Severe ROP	1.123	0.462-2.729	1.181	0.253-5.522	1.586	0.485-5.185	0.756	0.116-4.914
Laser surgery	1.515	0.582-3.944	1.015	0.207-4.969	1.304	0.381-4.463	1.163	0.175-7.736

Estimated ORs adjusted for both gestational age and birth weight, based on the logistic regression model.

*P value <0.05

Abbreviation: HC, histologic chorioamnionitis; aOR, adjusted odds ratio; BPD, bronchopulmonary dysplasia; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity

DISCUSSION

The primary findings of our study were the significant association of HC with a lower GA at birth and a reduced risk of RDS based on each disease criterion. Other outcomes were not associated with HC following adjustments for potential confounders, including GA and birth weight, based on each criterion.

Many studies have supported the idea that HC protects against RDS. Watterberg et al. [15] observed that the increased production of inflammatory cytokines and cortisol accelerate lung maturation and that this process decreases the incidence of RDS in a prospective study. However, an important issue to consider is that none of the infants in this study received antenatal steroids. Since the beginning of the era of antenatal steroid treatment, several studies have reexamined the effects of HC. Elimian et al. [16] studied infants with birth weights <1,750 g who were diagnosed with HC; they reported that the group treated with antenatal steroids had a significantly lower incidence of RDS compared with the group that was not treated with steroids. Lahra et al. [17] demonstrated that HC was associated with a significant reduction of RDS among infants <30 weeks gestation; chorioamnionitis with umbilical vasculitis, in particular, is associated with a markedly reduced incidence of RDS compared with chorioamnionitis alone. Other studies have also described a reduction of RDS among the HC-exposed preterm infants [3,4]. In those studies, the antenatal steroid exposure rate was not different between the HC-exposed and HC-unexposed infants. After adjusting for confounding

factors such as GA and birth weight, we established an independent relationship between HC and RDS for each criterion.

The relationship between chorioamnionitis and BPD is still controversial. The most recent evidence suggests that a maturational effect exerted by HC appears to decrease the incidence of RDS in preterm infants, but this effect also appears to contribute to the increased susceptibility of infants to postnatal lung injury [6,15,18,19]. A recent systematic review and meta-analysis by Hartling et al. [12] uncovered evidence of a relationship between BPD and chorioamnionitis. However, the adjusted results were no longer significant, and the conclusions were more conservative [12]. We could not find evidence of an effect exerted by HC on the incidence of BPD based on any of our criteria.

Neonatal sepsis, especially early-onset disease, is often associated with vertically transmitted infections. Several studies have reported that HC represents the risk of neonatal sepsis in very preterm infants [3,4,20]. However, other studies have failed to demonstrate a relationship between HC and neonatal sepsis [17]. In our study, HC was not associated with either early-onset or late onset sepsis.

IVH and PVL are common brain injuries in VLBW infants. Recently, Ylijoki et al. [21] performed a systematic review to evaluate the relationship between HC and brain lesions in preterm infants. In 11 of the 37 (30%) studies, no relationship was found; in 3 of the studies, HC was not associated with either IVH or PVL. However, 26 of the 37 (70%) publications found that HC was a

risk factor for the eventual development of brain abnormalities (IVH or PVL). They concluded that HC is not associated with a higher risk of brain injury in preterm infants compared with other underlying pathologies [21]. A recent systematic review and meta-analysis demonstrated that the use of antenatal steroids was associated with a decreased incidence of IVH in infants exposed to HC [22]. In our study, 87.8% of the infants with HC were exposed to antenatal steroid and HC was not related to the occurrence of IVH based on any criteria.

A number of studies have attempted to evaluate the relationship between HC and ROP. Dammann et al. [23] found evidence supporting the idea that extreme prematurity and multiple hits of perinatal inflammation may contribute to an increased risk of ROP. By contrast, Woo et al. [24] reported that neither HC nor funisitis were associated with ROP. A recent systematic review and meta-analysis [25] reported that chorioamnionitis was significantly associated with ROP of any stage and severe ROP (stage ≥3). However, the relationship disappeared upon further analysis of these studies following an adjustment for GA. Therefore, the authors concluded that chorioamnionitis cannot be considered a definitive risk factor for ROP [25]. Our study also found that HC was significantly associated with both severe ROP (≥ stage 3) and an increased incidence of laser surgery. However, the relationship disappeared upon further analysis following adjustments for both GA and birth weight. Our results are consistent with those of the meta-analysis.

The limitations of this study include a single center study and its retrospective nature. The strengths of the study include its use of criteria to diagnose HC via a consistent standardized placental assessment to determine both the severity of the inflammation and the extent of fetal involvement and the recent study period.

In conclusion, the results of this study indicate that HC significantly decreases the risk of RDS, while underscoring its little association with other morbidities. Further studies designed to evaluate the interactions of HC with various postnatal factors, as well as the independent role played by HC, are necessary.

REFERENCES

1 Yoon BH, Romero R, Park JS, Kim M, Oh SY, Kim CJ, Jun JK: The relationship among inflammatory lesions of the umbilical cord (funisitis), umbilical cord plasma interleukin 6 concentration, amniotic fluid infection, and neonatal sepsis. Am J Obstet Gynecol 2000;183:1124-1129.

2 Ramsey PS, Lieman JM, Brumfield CG, Carlo W: Chorioamnionitis increases neonatal morbidity in pregnancies complicated by preterm premature rupture of membranes. Am J Obstet Gynecol 2005;192:1162-1166.

3 Dempsey E, Chen MF, Kokottis T, Vallerand D, Usher R: Outcome of neonates less than 30 weeks gestation with histologic chorioamnionitis. Am J Perinatol 2005;22:155-159.

4 Andrews WW, Goldenberg RL, Faye-Petersen O, Cliver S, Goepfert AR, Hauth JC: The alabama preterm birth study: Polymorphonuclear and mononuclear cell placental infiltrations, other markers of inflammation, and outcomes in 23- to 32-week preterm newborn infants. Am J Obstet Gynecol 2006;195:803-808.

5 Thomas W, Speer CP: Chorioamnionitis: Important risk factor or innocent bystander for neonatal outcome? Neonatology 2011;99:177-187.

6 Speer CP: Neonatal respiratory distress syndrome: An inflammatory disease? Neonatology 2011;99:316-319.

7 Erdemir G, Kultursay N, Calkavur S, Zekioglu O, Koroglu OA, Cakmak B, Yalaz M, Akisu M, Sagol S: Histological chorioamnionitis: Effects

on premature delivery and neonatal prognosis. Pediatr Neonatol 2013;54:267-274.

8 Soraisham AS, Trevenen C, Wood S, Singhal N, Sauve R: Histological chorioamnionitis and neurodevelopmental outcome in preterm infants. J Perinatol 2013;33:70-75.

9 Lee HJ, Kim EK, Kim HS, Choi CW, Kim BI, Choi JH: Chorioamnionitis, respiratory distress syndrome and bronchopulmonary dysplasia in extremely low birth weight infants. J Perinatol 2011;31:166-170.

10 Jessop F, Sebire N: Histologic chorioamnionitis: Current concepts of diagnosis classification and clinical significance. Fetal and Maternal Medicine Review 2011;22:25-44.

11 Park CW, Moon KC, Park JS, Jun JK, Romero R, Yoon BH: The involvement of human amnion in histologic chorioamnionitis is an indicator that a fetal and an intra-amniotic inflammatory response is more likely and severe: Clinical implications. Placenta 2009;30:56-61.

12 Hartling L, Liang Y, Lacaze-Masmonteil T: Chorioamnionitis as a risk factor for bronchopulmonary dysplasia: A systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2012;97:F8-F17.

13 Salafia CM, Weigl C, Silberman L: The prevalence and distribution of acute placental inflammation in uncomplicated term pregnancies. Obstet Gynecol 1989;73:383-389.

14 Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, Brotherton T: Neonatal necrotizing enterocolitis. Ann Surg 1978;187:1-7.

15 Watterberg KL, Demers LM, Scott SM, Murphy S: Chorioamnionitis and early lung inflammation in infants in whom bronchopulmonary dyslasia develops. Pediatrics 1996;97:210-215.

16 Elimian A, Verma U, Beneck D, Cipriano R, Visintainer P, Tejani N: Histologic chorioamnionitis, antenatal steroids, and perinatal outcomes. Obstet Gynecol 2000;96:333-336.

17 Lahra MM, Beeby PJ, Jeffery HE: Maternal versus fetal inflammation and respiratory distress syndrome: A 10-year hospital cohort study. Arch Dis Child Fetal Neonatal Ed 2009;94:F13-16.

18 Been JV, Rours IG, Kornelisse RF, Jonkers F, de Krijger RR, Zimmermann LJ: Chorioamnionitis alters the response to surfactant in preterm infants. J Pediatr 2010;156:10-15.

19 Plakkal N, Soraisham AS, Trevenen C, Freiheit EA, Sauve R: Histological chorioamnionitis and bronchopulmonary dysplasia: A retrospective cohort study. J Perinatol 2013;33:441-445.

20 Hendson L, Russell L, Robertson CM, Liang Y, Chen Y, Abdalla A, Lacaze-Masmonteil T: Neonatal and neurodevelopmental outcomes of very low birth weight infants with histologic chorioamnionitis. J Pediatr 2011;158:397-402.

21 Ylijoki M, Ekholm E, Haataja L, Lehtonen L, Pipari study group: Is chorioamnionitis harmful for the brain of preterm infants? A clinical overview. Acta Obstet Gynecol Scand 2012;91:403-419.

22 Been JV, Degraeuwe PL, Kramer BW, Zimmermann LJ: Antenatal steroids and neonatal outcome after chorioamnionitis: A meta-analysis. BJOG 2011;118:113-122.

23 Dammann O, Brinkhaus MJ, Bartels DB, Dordelmann M, Dressler F, Kerk J, Dork T, Dammann CE: Immaturity, perinatal inflammation, and retinopathy of prematurity: A multi-hit hypothesis. Early Hum Dev 2009;85:325-329.

24 Woo SJ, Park KH, Jung HJ, Kim S, Choe G, Ahn J, Park KH: Effects of maternal and placental inflammation on retinopathy of prematurity. Graefes Arch Clin Exp Ophthalmol 2012;250:915-923.

25 Mitra S, Aune D, Speer CP, Saugstad OD: Chorioamnionitis as a risk factor for retinopathy of prematurity: A systematic review and meta-analysis. Neonatology 2014;105:189-199.

국문 초록

목표: 태반의 염증의 정도와 부위에 따른 임상적 영향을 평가하기 위해 만든 다양한 진단 기준으로 조직학적 융모양막염을 정의하고, 각 진단 기준에 따른 조직학적 융모양막염이 극소 저체중 출생아의 신생아기 질환의 유병률에 미치는 영향을 파악하고자 한다.

방법: 2008년 1월부터 2012년 12월까지 분당서울대학교병원에서 출생하여 신생아 중환자실에 입원하였던 출생 체중 1,500 g 미만의 조산아 261명을 대상으로 의무기록 분석을 통한 후향적 연구를 시행하였다. 태반의 염증의 정도에 따른 태아에 미치는 영향을 반영하고자, 태반의 조직학적 검사를 통해 다형핵백혈구의 침범 부위에 따라 네 개의 진단 기준을 만들었다. 각 진단 기준에 의한 조직학적 융모양막염의 유무에 따라 신생아기 주요 질환의 유병률을 비교하였다.

결과: 어떠한 진단 기준을 사용하여도 조직학적 융모양막염에 노출된 군이 노출되지 않은 군에 비해 유의하게 평균 재태 연령이 낮았다. 평균 출생 체중과 성별은 각 군간에 차이가 없었다. 진단 기준 2에 의해 진단한 조직학적 융모양막염에 노출된 군에서 기관지폐형성증의 유병률이 높았으며, 진단 기준 1과 3을 이용하여 진단한 조직학적 융모양막염이 3단계 이상의 중증 미숙아 망막병증 및 레이저 치료를 요했던 경우와 유의하게 연관성이 있었다. 그러나

재태 연령과 출생 체중을 보정한 회귀 분석에서 이러한 연관성은 통계적 유의성이 없는 것으로 나타났다. 재태 연령과 출생 체중을 보정한 회귀분석에서 신생아 호흡곤란 증후군만 모든 진단 기준에 따른 조직학적 융모양막염과 연관성이 있었다. 다른 신생아 질환들의 유병률은 조직학적 융모양막염과 유의한 연관성을 보이지 않았다.

결론: 조직학적 융모양막염은 신생아 호흡곤란 증후군의 위험도를 줄이는 유의한 결과를 보였으며, 이것은 조직학적 융모양막염의 임상적 영향을 충분히 반영한 것으로 생각된다. 반면 조직학적 융모양막염과 다른 신생아기 주요 질환과의 연관성은 뚜렷하지 않은 것으로 보여진다.

주요어 : 융모양막염; 조직학적 융모양막염; 제대염; 신생아기 질환; 극소 저체중 출생아; 미숙아

학 번 : 2013-22596