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The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: informahealthcare.com/journals/ijmf20

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To cite this article: Seung Mi Lee, Roberto Romero, Kyung A. Lee, Hye Jin Yang, Kyung Joon Oh, Chan-Wook Park & Bo Hyun Yoon (2011) The frequency and risk factors of funisitis and histologic chorioamnionitis in pregnant women at term who delivered after the spontaneous onset of labor, The Journal of Maternal-Fetal & Neonatal Medicine, 24:1, 37-42, DOI: 10.3109/14767058.2010.482622

To link to this article: https://doi.org/10.3109/14767058.2010.482622

Published online: 10 Aug 2010.

The Journal of Maternal-Fetal and Neonatal Medicine, January 2011; 24(1): 37–42

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The frequency and risk factors of funisitis and histologic chorioamnionitis in pregnant women at term who delivered after the spontaneous onset of labor

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(Received 10 February 2010; accepted 24 February 2010)

Abstract

Objective. To examine the frequency and risk factors of funisitis and histologic chorioamnionitis in the placentas of term pregnant women who delivered after the spontaneous onset of labor.

Methods. The frequency of funisitis and histologic chorioamnionitis was examined in consecutive pregnant women at term with singleton pregnancies who delivered after the spontaneous onset of labor. Nonparametric statistics were used for data analysis.

Results. (1) The frequency of funisitis and histologic chorioamnionitis was 6.7% (88/1316) and 23.6% (310/1316), respectively; (2) Patients with funisitis had significantly higher rates of nulliparity, regional analgesia, operative vaginal delivery, longer duration of labor and rupture of membranes (ROM), and higher gestational age and birthweight than those without funisitis ($p < 0.05$ for each); (3) Patients with histologic chorioamnionitis had significantly higher rates of nulliparity, oxytocin augmentation, regional analgesia, cesarean section or operative vaginal delivery, longer duration of labor and ROM, and higher gestational age and birthweight than those without histologic chorioamnionitis ($p < 0.05$ for each); (4) Multiple logistic regression analysis indicated that the longer the duration of labor, the higher the risk of funisitis, and that nulliparity and the duration of labor significantly increased the odds of histologic chorioamnionitis ($p < 0.05$ for each).

Conclusion. The longer the duration of labor, the higher the risk of funisitis and histologic chorioamnionitis in pregnant women at term who delivered after the spontaneous onset of labor.

Keywords: *infection, inflammation, nulliparity, duration of labor, prolonged labour, rupture of membranes, pregnancy*

Introduction

Funisitis (inflammation of the umbilical cord) is the histologic hallmark of the fetal inflammatory response, and histologic chorioamnionitis represents a maternal inflammatory response [1]. These lesions are identified in the placentas of neonates born preterm as well as at term, and their presence is associated with increased neonatal morbidity and cerebral palsy [2–8]. Recent reports have indicated that histologic chorioamnionitis at term is associated with placental abruption, meconium-stained amniotic fluid, severe pulmonary hypertension in term neonates, and fetal growth restriction [9–12].

We have previously demonstrated that funisitis and histologic chorioamnionitis are associated with intra-amniotic infection/inflammation, and that those lesions are more frequent in women in labor [13,14]. Moreover, the greater the degree of cervical dilatation at the time of cesarean section, the higher the risk of histologic chorioamnionitis in patients with intact membranes. The increased risk of intrauterine infection and inflammation has been attributed to a 'suction-like' effect of uterine contractions, whereby vaginal fluid can ascend into the uterine cavity during the course of labor [15]. Our previous studies [13,14] allowed the examination of the relationship between funisitis/histologic chorioamnionitis and amniotic fluid culture results and intraamniotic inflammation because fluid was collected at the time of cesarean delivery or within 72 h of delivery.

The next important question is the frequency of and risk factors for funisitis and histologic chorioamnionitis in women who delivered after the spontaneous onset of labor at term. This study was conducted to address this question.

Methods

Study design

The frequency of funisitis and histologic chorioamnionitis was examined in consecutive pregnant women who delivered term singleton neonates (gestational age at delivery between 37 and 42 weeks) after the spontaneous onset of labor at the Seoul National University Hospital between January 2003 and December 2006. Cases with fetal anomalies or fetal death, women in whom labor was induced and those who were delivered before the onset of labor by cesarean section were excluded. The Institutional Review Board of the Seoul National University Hospital

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ISSN 1476-7058 print/ISSN 1476-4954 online © 2011 Informa UK, Ltd.
DOI: 10.3109/14767058.2010.482622

approved the review of medical charts and pathologic reports for the purposes of research. The Seoul National University has a Federal Wide Assurance with the Office for Human Research Protections of the Department of Health and Human Services of the United States.

Placental examination

The placentas from patients enrolled in this study were obtained after delivery. The following sites were sampled: chorion-amnion, the chorionic plate and the umbilical cord. These samples were fixed in 10% neutral buffered formalin and embedded in paraffin. Sections of tissue blocks were stained with hematoxylin and eosin. Histologic chorioamnionitis was defined as the presence of acute inflammatory changes on examination of a membrane roll and chorionic plate of the placenta; funisitis was diagnosed in the presence of neutrophil infiltration into the umbilical vessel walls or Wharton's jelly, according to criteria previously published by our group [3].

Statistical analysis

Proportions were compared with Fisher's exact test or Chi-square test for trend and comparisons of continuous variables between groups were performed with Mann–Whitney *U*-tests as appropriate. Logistic regression was conducted for multivariate analysis. A p-value of <0.05 was considered significant.

Results

During the study period, 1359 singleton pregnant women delivered term live neonates (gestational age at delivery between 37 and 42 weeks) without major anomalies after the spontaneous onset of labor. Among these women, the results of histopathologic examination of the placenta were not available in 43 women. A total of 1316 cases was included in this study.

Funisitis and histologic chorioamnionitis were diagnosed in 6.7% (88/1316) and 23.6% (310/1316) of cases, respectively. Acute inflammation was detected in the following tissues: 4.5% in amnion, 23.1% in chorion-decidua, 3.9% in the chorionic plate, and 6.7% in the umbilical cord.

Table I compares the clinical characteristics and pregnancy outcomes of the study population according to the presence or absence of funisitis. Patients with funisitis had a higher rate of nulliparity, longer duration of labor and rupture of membranes (ROM), and had received

Table I. Clinical characteristics and pregnancy outcomes according to the presence or absence of funisitis.

	Funisitis		
	Absent ($n=1228$)	Present ($n=88$)	p Value
Clinical characteristics			
Age (years)*	31.1 ± 3.4	31.1 ± 3.6	NS
Nulliparity	679 (55.3%)	63 (71.6%)	<0.005
Maternal age ≥ 35 years old	179 (14.6%)	13 (14.8%)	NS
Hypertensive disease in pregnancy	21 (1.7%)	1 (1.1%)	NS
Diabetes	15 (1.2%)	0 (0%)	NS
Duration of ROM (hours)*	5.3 ± 10.1	7.8 ± 14.2	<0.05
Total duration of labor (hours)*,†	3.4 ± 2.9	5.9 ± 3.6	<0.001
Duration of 1st stage of labor (hours)*,†	2.5 ± 2.4	4.6 ± 3.1	<0.001
Duration of 2nd stage of labor (hours)*,†	0.9 ± 0.9	1.3 ± 1.3	<0.005
Use of oxytocin augmentation	384 (31.3%)	35 (39.8%)	NS
Use of epidural analgesia	423 (34.4%)	45 (51.1%)	<0.005
Pregnancy outcomes			
Gestational age (weeks)*	39.7 ± 1.0	39.9 ± 1.0	<0.05
Birth weight(g)*	3266 ± 384	3396 ± 405	<0.01
Birth weight > 4000 g	39 (3.2%)	8 (9.1%)	<0.05
Small-for-gestational age neonates	81 (6.6%)	4 (4.5%)	NS
Large-for-gestational age neonates	137 (11.2%)	15 (17.0%)	NS
Cesarean delivery	52 (4.2%)	8 (9.1%)	0.056
Cesarean delivery due to failure to progress	40 (3.3%)	6 (6.8%)	NS
Cesarean delivery due to fetal distress	11 (0.9%)	2 (2.3%)	NS
Operative vaginal delivery	148 (12.1%)	18 (20.5%)	<0.05
1-Min Apgar score < 7	28 (2.3%)	3 (3.4%)	NS
5-Min Apgar score < 7	10 (0.8%)	0 (0%)	NS
Positive meconium staining at birth	243 (19.8%)	43 (48.9%)	<0.001
pH of umbilical artery at birth*	7.282 ± 0.060	7.267 ± 0.061	<0.01
Base excess of umbilical artery at birth (mmol/l)*	(−4.148) ± 2.694	(−5.052) ± 2.882	<0.005
pO_2 of umbilical artery at birth (mmHg)*	20.224 ± 9.324	18.793 ± 6.443	<0.05
Saturation of O_2 in umbilical artery at birth (%)*	31.634 ± 15.472	28.885 ± 15.856	<0.05
NICU admission	21 (1.7%)	4 (4.5%)	0.08

ROM, rupture of membranes; NS, not significant.

*Values are given as mean ± standard deviation.

†Duration of labor was analyzed only in cases who admitted before cervical dilatation of 4 cm; duration of 1st stage was defined as duration of cervical dilatation from 4 to 10 cm; duration of 2nd stage was defined as duration between full cervical dilatation and fetal delivery.

regional anesthesia more frequently than those without funisitis ($p < 0.05$ for each). However, there was no significant difference in the mean maternal age, proportions of complicated pregnancies and oxytocin augmentation between the two groups of cases. Patients with funisitis had a significantly higher gestational age and birthweight and higher rates of neonates with a birthweight of >4000 g, and operative vaginal delivery than those without funisitis ($p < 0.05$ for each). However, there was no significant difference in the rate of small-for-gestational age (SGA) neonates, large for gestational age (LGA) and cesarean delivery between the two groups of cases. Neonates born to mothers with funisitis had a higher rate of meconium-stained amniotic fluid (MSAF) at birth and lower pH and base excess than those born to mothers without funisitis ($p < 0.05$ for each). The rate of neonatal intensive care unit (NICU) admissions was higher in neonates born to mothers with funisitis than those without funisitis, but without reaching statistical significance ($p = 0.08$). The association between funisitis and MSAF remained significant after adjusting for the duration of labor and the duration of ROM ($p < 0.001$).

Table II describes the clinical characteristics and pregnancy outcomes of the study population according to the presence or absence of histologic chorioamnionitis. Patients with histologic chorioamnionitis had a higher rate of nulliparity, longer duration of labor and ROM and received regional anesthesia and oxytocin augmentation more frequently than those without histologic chorioamnionitis ($p < 0.001$ for each). However, there was no significant difference in the mean maternal age and proportions of complicated pregnancies between the two groups of cases ($p > 0.1$). Patients with histologic chorioamnionitis had significantly higher gestational age and birthweights and higher rates of neonates with a birthweight of >4000 g, cesarean delivery, cesarean delivery due to failure to progress during labor, and operative vaginal delivery than those without histologic chorioamnionitis ($p < 0.05$ for each). However, there was no significant difference in the rate of SGA neonates and cesarean delivery due to fetal distress between the two groups of cases ($p > 0.1$). Neonates born to mothers with histologic chorioamnionitis had higher rates of MSAF at birth and lower pH and base excess than those born to mothers without histologic chorioamnionitis ($p < 0.05$ for each). However, the risk of NICU admission was not different between the two groups.

Multiple logistic regression analysis indicated that the odds of funisitis increased with the longer duration of labor ($p < 0.001$, Table III). Nulliparity, the duration of ROM,

Table II. Clinical characteristics and pregnancy outcomes according to the presence or absence of histologic chorioamnionitis.

	Histologic chorioamnionitis		
	Absent ($n = 1006$)	Present ($n = 310$)	p Value
Clinical characteristics			
Age (years)*	31.1 ± 3.5	31.0 ± 3.4	NS
Nulliparity	524 (52.1%)	218 (70.3%)	<0.001
Maternal age ≥ 35 years old	149 (14.8%)	43 (13.9%)	NS
Hypertensive disease in pregnancy	18 (1.8%)	4 (1.3%)	NS
Diabetes	14 (1.4%)	1 (0.3%)	NS
Duration of ROM (hours)*	4.8 ± 8.4	7.6 ± 15.1	<0.001
Total duration of labor (hours)*,†	3.1 ± 2.7	4.9 ± 3.4	<0.001
Duration of 1st stage of labor (hours)*,†	2.3 ± 2.3	3.6 ± 2.9	<0.001
Duration of 2nd stage of labor (hours)*,†	0.8 ± 0.8	1.3 ± 1.2	<0.001
Use of oxytocin augmentation	288 (28.6%)	131 (42.3%)	<0.001
Use of epidural analgesia	313 (31.1%)	155 (50.0%)	<0.001
Pregnancy outcomes			
Gestational age (weeks)*	39.6 ± 1.0	39.8 ± 0.9	<0.005
Birth weight(g)*	3258 ± 383	3331 ± 393	<0.05
Birth weight > 4000 g	27 (2.7%)	20 (6.5%)	<0.005
Small-for-gestational age neonates	70 (7.0%)	15 (4.8%)	NS
Large-for-gestational age neonates	106 (10.5%)	46 (14.8%)	<0.05
Cesarean delivery	35 (3.5%)	25 (8.1%)	<0.005
Cesarean delivery due to failure to progress	24 (2.4%)	22 (7.1%)	<0.001
Cesarean delivery due to fetal distress	10 (1.0%)	3 (1.0%)	NS
Operative vaginal delivery	111 (11.0%)	55 (17.7%)	<0.005
1-Min Apgar score < 7	26 (2.6%)	5 (1.6%)	NS
5-Min Apgar score < 7	10 (1.0%)	0 (0%)	NS
Positive meconium staining at birth	193 (19.2%)	93 (30.0%)	<0.001
pH of umbilical artery at birth*	7.283 ± 0.061	7.277 ± 0.060	<0.05
Base excess of umbilical artery at birth (mmol/l)*	(−4.14) ± 2.72	(−4.44) ± 2.70	<0.05
pO_2 of umbilical artery at birth (mmHg)*	20.282 ± 9.187	19.625 ± 9.078	<0.05
Saturation of O_2 in umbilical artery at birth (%)*	31.926 ± 15.604	29.922 ± 15.119	<0.05
NICU admission	19 (1.9%)	6 (1.9%)	NS

ROM, rupture of membranes; NS, not significant.

*Values are given as mean ± standard deviation.

†Duration of labor was analyzed only in cases who admitted before cervical dilatation of 4 cm; duration of 1st stage was defined as duration of cervical dilatation from 4 to 10 cm; duration of 2nd stage was defined as duration between full cervical dilatation and fetal delivery.

Table III. Relationship of various independent antepartum risk factors with funisitis and histologic chorioamnionitis, analyzed by overall logistic regression analysis.

Variables	Odds ratio	95% Confidence interval	Significance
Funisitis			
Nulliparity	1.354	0.697–2.629	NS
Total duration of labor	1.208	1.110–1.316	<0.001
Duration of ROM	1.006	0.987–1.025	NS
Use of oxytocin augmentation	0.683	0.382–1.221	NS
Use of epidural analgesia	0.964	0.516–1.800	NS
Gestational age	1.193	0.902–1.578	NS
Large-for-gestational age neonates	1.299	0.649–2.599	NS
Cesarean delivery	0.755	0.259–2.198	NS
Operative vaginal delivery	1.432	0.760–2.701	NS
Histologic chorioamnionitis			
Nulliparity	1.549	1.070–2.243	<0.05
Total duration of labor	1.133	1.069–1.201	<0.001
Duration of ROM	1.003	0.990–1.016	NS
Use of oxytocin augmentation	0.996	0.711–1.396	NS
Use of epidural analgesia	1.135	0.788–1.634	NS
Gestational age	1.124	0.959–1.318	NS
Large-for-gestational age neonates	1.391	0.886–2.183	NS
Cesarean delivery	1.327	0.682–2.580	NS
Operative vaginal delivery	1.144	0.753–1.741	NS

NS, not significant; ROM, rupture of membranes.

use of regional anesthesia and oxytocin augmentation, gestational age, LGA, cesarean delivery, and operative vaginal delivery were not significantly associated with funisitis after adjusting for confounding variables.

The frequency of histologic chorioamnionitis was associated with nulliparity and the longer duration of labor by logistic regression analysis (Table III for odds ratios, $p < 0.05$). The duration of ROM, use of regional anesthesia and oxytocin augmentation, gestational age, LGA, cesarean delivery, and operative vaginal delivery were not significantly associated with histologic chorioamnionitis after adjusting for confounding variables (Table III).

Figure 1 illustrates that the frequency of funisitis and histologic chorioamnionitis increases significantly as a function of the duration of labor. Both inflammatory lesions were more common as the duration of labor increased ($p < 0.001$ for each, χ^2 test for trend).

Discussion

Principal findings of the study

(1) The frequency of funisitis and histologic chorioamnionitis in term pregnant women with spontaneous onset of labor was 7% and 24%, respectively; (2) the risk of funisitis increased with the duration of labor; (3) the risk of histologic chorioamnionitis increased with nulliparity and the duration of labor.

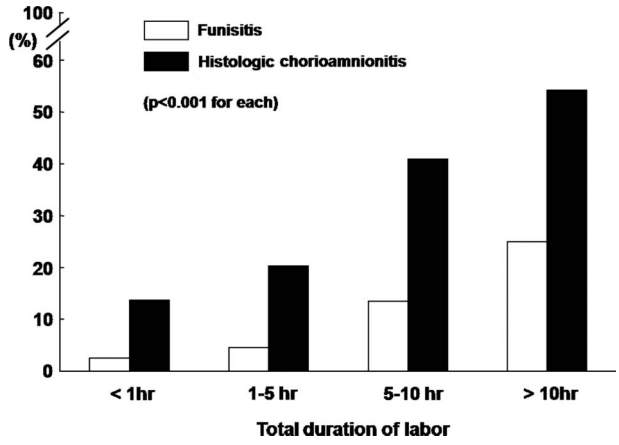

Figure 1. The frequency of funisitis and histologic chorioamnionitis as a function of total duration of labor. The frequency of funisitis (□) and histologic chorioamnionitis (■) increased according to the total duration of labor ($p < 0.001$ for each; χ^2 test for trend).

The duration of labor and the risk of funisitis and histologic chorioamnionitis

The significant relationship between labor and the risk of funisitis and histologic chorioamnionitis is in keeping with previous studies reporting an association between the presence and progress of labor and the risk of intraamniotic infection, intraamniotic inflammation, and funisitis or histologic chorioamnionitis [13,14,16–22]. Moreover, we demonstrated that the risk of funisitis and histologic chorioamnionitis increased gradually according to the duration of labor (Figure 1 and Table III). This has not been fully evaluated in other previous studies [13,14,16–28]. This association between labor and risk of placental inflammation may be attributed to the so-called suction-like effect of uterine contractions, which allow vaginal fluid containing a large microbial load to ascend into the uterine cavity [15].

The duration of ROM and the risk of funisitis and histologic chorioamnionitis

In previous reports, there was a significant relationship between the duration of ROM and the risk of histologic chorioamnionitis in cases with term PROM or preterm PROM [29–31]. However, we were not able to demonstrate a significant association between the duration of ROM and funisitis or histologic chorioamnionitis after adjusting for other confounding variables, indicating that the relationship between the duration of ROM and the risk of funisitis or histologic chorioamnionitis might result from longer duration of labor in women with longer duration of ROM (Table III). Moreover, in a recent study performed in patients with preterm PROM, the duration of preterm PROM did not affect the rate of intra-amniotic inflammation [32]. This evidence might suggest that the suction-like effect of uterine contractions be the necessary condition for the funisitis or histologic chorioamnionitis, rather than ruptured membranes [15].

The strength of this study

The reported frequency of funisitis and histologic chorioamnionitis at term varies among studies [13,14,17,23–28 ,30].

This has been attributed to differences in the diagnostic criteria and the study populations. We were unable to find a study which examined the relationship between the parity, the duration of labor and the risk of funisitis or histologic chorioamnionitis in women at term who delivered after the spontaneous onset of labor in consecutive series.

The clinical significance of funisitis at term

Previous studies have demonstrated that funisitis is associated with adverse perinatal outcome in preterm neonates [2–8]. However, the clinical significance of funisitis at term has not been well determined. In this study, funisitis was significantly associated with MSAF, lower pH and base excess and associated with NICU admission with marginal significance. This association might be, in part, attributed to the longer duration of labor in patients with funisitis, because prolonged duration of labor was associated with lower cord pH at birth and adverse perinatal outcome in previous reports [33,34]. However, the association between funisitis and MSAF remained significant, even after adjusting for the duration of labor ($p < 0.001$), although the difference in cord pH at birth and the rate of NICU admission between patients with and without funisitis became insignificant after adjusting for the duration of labor. This strong relationship between funisitis and MSAF is consistent with the results of previous reports [11,35,36]. Romero et al. [35] reported an association between MSAF and microbial invasion of amniotic fluid in preterm delivery, and Rao et al. [11] reported higher incidence of MSAF in patients with chorioamnionitis and/or funisitis in near-term or term. Burgess et al. [36] also reported an association between inflammation of the umbilical cord and meconium passage *in utero* in autopsied cases.

The high frequency of histologic chorioamnionitis in term gestation with spontaneous labor

It must be stressed that the frequency of histologic chorioamnionitis in the current study was common, and interpretation of clinical significance of histologic chorioamnionitis needs caution considering this high frequency. The presence of histologic chorioamnionitis in 24% of women may not represent pathology. After excluding cases with funisitis ($n = 88$), cases with histologic chorioamnionitis but without funisitis ($n = 231$) had comparable neonatal outcome to cases without placental inflammation (without histologic chorioamnionitis or funisitis, $n = 997$) in terms of Apgar score, blood gas analysis of cord arterial blood, and admission to NICU. Although the frequency of meconium staining in cases with histologic chorioamnionitis without funisitis was higher than in cases without placental inflammation with marginal significance ($p = 0.067$), this difference become insignificant after adjusting for the total duration of labor ($p > 0.2$). Of note, histologic chorioamnionitis without funisitis was also associated with nulliparity and total duration of labor, and this difference remained statistically significant even after adjusting for confounding variables ($p < 0.05$).

Mild histologic chorioamnionitis may reflect the insults of labor in the chorioamniotic membranes, particularly in the chorio-decidual interface, which must separate before delivery. It is tempting to postulate that inflammation is a mechanism through which that separation occurs in a select group of patients. It is also possible that the higher frequency of inflammatory lesions is unrelated to infection and microbial ascension into the uterine cavity, but represents a physiologic response to the labor process, or an inherent part of parturition. A recent study [37] using genome-wide expression profiling has demonstrated a molecular signature of inflammation in the chorioamniotic membranes of patients who had spontaneous labor and vaginal delivery, when compared to a control group of women not in labor. It is interesting that such a molecular signature was found even in patients without any evidence of histologic chorioamnionitis.

Is funisitis/histologic chorioamnionitis the cause or consequence of labor?

The relationship between the duration of labor and the frequency of funisitis or histologic chorioamnionitis favors the interpretation that placental inflammation develops during the course of labor. It is possible that in a small fraction of patients, intrauterine infection, which may have accidentally occurred at term, contributes to the initiation of labor. However, we believe that this must be a rare phenomenon because the rate of microbiologically-proven intraamniotic infection is extremely low in women at term not in labor, and even in women in early labor [13].

In conclusion, the frequency of funisitis and histologic chorioamnionitis increases with the duration of labor in pregnant women at term delivered after the spontaneous onset of labor.

Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (No. 2009-0080429) and in part by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH, DHHS.

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