Published in final edited form as:

Placenta. 2010 September ; 31(9): 792–795. doi:10.1016/j.placenta.2010.06.013.

Histologic chorioamnionitis is more common after spontaneous labor than after induced labor at term

Hyun Soo PARK, MD^a, Roberto ROMERO, MD^b, Seung Mi LEE, MD^c, Chan-Wook PARK, MD, PhD^c, Jong Kwan JUN, MD, PhD^c, Bo Hyun YOON, MD, PhD^c

^aDepartment of Obstetrics and Gynecology, Graduate School of Medicine, Dongguk University, Seoul, Korea

^bPerinatology Research Branch, NICHD/NIH/DHHS, Bethesda, MD, and Detroit, MI, USA; Department of Obstetrics and Gynecology and Center for Molecular Medicine and Genetics, Wayne State University, Detroit, MI, USA

^cDepartment of Obstetrics and Gynecology, Seoul National University College of Medicine

Abstract

OBJECTIVE—Inflammation of the chorioamniotic membranes (histologic chorioamnionitis) is a risk factor for adverse neonatal outcome. Labor has many common features with inflammatory processes; therefore, an important question is whether the frequency of histologic chorioamnionitis in spontaneous labor at term is higher than that of women in labor after induction. This study was conducted to address this question.

STUDY DESIGN—The frequency of histologic chorioamnionitis was compared between patients who delivered after the spontaneous onset of labor versus in those who delivered after induction of labor at term in singleton gestations (> 37 weeks). Patients in whom uterotonic agents were used during the latent phase of labor were excluded.

RESULTS—1) The overall frequency of histologic chorioamnionitis was 20.2% (107/531); 2) histologic chorioamnionitis was significantly more frequent in women who delivered after the spontaneous onset of labor than in those who underwent induction of labor (24.3% [81 of 333] vs 13.1% [26/198], $p < 0.005$). This difference remained significant after adjusting for parity, gestational age at delivery, total duration of labor, the interval from rupture of membranes to delivery and the mode of delivery.

CONCLUSION—Histologic chorioamnionitis is more common in women who delivered after the spontaneous onset of labor than in those who underwent induction of labor at term.

Correspondence to: Bo Hyun Yoon, MD, PhD, Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, 110-744, Korea. Tel: 82-2-760-2826, Fax: 82-2-765-3002, yoonbh@snu.ac.kr.

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Keywords

Placental inflammation; Parturition; Spontaneous onset of labor; Term pregnancy; Inflammation; Infection

INTRODUCTION

Histologic chorioamnionitis is frequently diagnosed in placentas delivered at term and in preterm gestations, and is a risk factor for the occurrence of infection-related and non-infection related perinatal and maternal morbidity and mortality [1–6]. Recent studies indicate that histologic chorioamnionitis is significantly more common in patients with spontaneous preterm birth than in those with indicated preterm birth (60% vs 9%) [7]. However, there is a paucity of information about the risk of histologic chorioamnionitis according to the type of labor (i.e., spontaneous onset versus induction of labor) in term gestations. This study was performed to examine this question.

MATERIALS AND METHODS

Study design

Histologic examination of the placenta was performed in patients who delivered live term singleton neonates (gestational age from 37+0weeks to 42+0weeks) after labor between October 2004 and October 2005 at the Seoul National University Hospital. Patients were divided into 2 groups according to the onset of labor before delivery, regardless of the mode of delivery: group 1 included women who delivered after the spontaneous onset of labor (n=333), and group 2 included women who delivered after the induction of labor (n=198). Cesarean delivery was performed for obstetrical indications during labor. Group 2 consisted of patients whose labor was induced using oxytocin and/or prostaglandin E1 (misoprostol, Pfizer Pharmaceuticals Korea, Seoul, Korea) or prostaglandin E2 (dinoprostone pessary, Bukwang Pharmaceutical, Seoul, Korea). Patients in whom uterotonic agents (oxytocin or prostaglandin) were used during the latent phase of labor (cervical dilatation less than 4cm) after the spontaneous onset of labor were excluded from the analysis because these cases represent neither group 1 (spontaneous onset of labor) nor group 2 (induced labor) and could possibly confound the results. Patients in whom oxytocin was used in the active phase of labor (cervical dilatation more than 4 cm) after spontaneous onset of labor were included in group 1.

Partograms are routinely used in our unit to plot changes in cervical dilatation and fetal descent. Given the difficulties in determining when labor begins, we chose to calculate the duration of labor from the onset of the active phase of labor, which was defined as 4cm of dilatation. The duration of the active phase of labor, as well as the second stage, was assessed using the partograms. The Institutional Review Board of the Seoul National University approved the collection and use of the information for research purposes. The Seoul National University has a Federal Wide assurance negotiated with the Office for Human Research Protection of the Department of Health and Human Services of the United States.

Histologic chorioamnionitis

Placentas were subjected to histopathologic evaluation. 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 described in detail [8]. Briefly, the inflammation of amnion and chorio-decidua was defined as the presence of at least one focus of more than 5 neutrophils and considered as severe inflammation if there is diffuse neutrophil infiltration. The inflammation of the chorionic plate was defined as the presence of at least one focus of 10 or more neutrophil foci or diffuse inflammation in the subchorionic fibrin, and considered as severe inflammation if there was diffuse and dense infiltration of neutrophils into the connective tissue of the chorionic plate, or placental vasculitis. Funisitis was defined as neutrophil infiltration confined to umbilical vessel walls and considered as severe funisitis if there was extensive neutrophil infiltration into Wharton's jelly.

Statistical analysis

Proportions were compared with the use of Chi-square test or Fisher's exact test as appropriate. Continuous variables were compared with the use of Student t-tests. Logistic regression analysis was performed to evaluate the contributing factors to the occurrence of histologic chorioamnionitis. $P < 0.05$ was considered significant.

RESULTS

Study population

A total of 738 patients delivered live newborns at term during the study period. One hundred sixty nine neonates were delivered before the onset of labor by cesarean delivery and 38 patients in whom the uterotonics were used during the latent phase of labor were excluded. Histologic examination of placenta was not available in 2 patients, of whom one patient delivered by cesarean section before the onset of labor and the other patient delivered with uterotonics used during the latent phase of labor. A total of 531 patients met the inclusion criteria.

Table 1 compares the clinical characteristics of mothers and neonates. Patients who delivered after the spontaneous onset of labor had a significantly lower mean gestational age at delivery, a shorter time interval between rupture of membranes and delivery and lower rate of nulliparity than those who delivered after induction of labor ($p < 0.05$). However, there were no significant differences in the mean duration of labor and birth weight between the two groups of patients ($p > 0.05$, Table 1). Cesarean delivery was significantly more frequent in group 2 ($p < 0.05$). The frequency of maternal fever on the day of delivery was higher in group 2 than in group 1 although the difference was not statistically significant ($p = 0.06$).

The indications for induction of labor were: 1) post-term pregnancy ($n=57$); 2) premature rupture of membranes ($n=42$); 3) maternal medical diseases ($n=37$); 4) fetal indications ($n=19$) including fetal growth restriction, non-reassuring fetal status or fetal anomalies; 5) oligohydramnios ($n=17$); and 6) others ($n=26$).

Frequency and distribution of histologic chorioamnionitis

The overall frequency of histologic chorioamnionitis was 20.2% (107/531, Table 2). Histologic chorioamnionitis was more common in women who delivered after the spontaneous onset of labor (group 1) than in those delivered after the induction of labor (group 2) (24.3% vs 13.1%, $p<0.005$).

The chorio-decidual interface was the most frequent site of inflammation, and the differences were significant between groups (group 1; 24.3% [81/333] vs group 2; 13.1% [26/198], $p<0.005$). The frequency of inflammation in amnion, umbilical cord, and chorionic plate were not significantly different between group 1 and 2.

We compared the frequency of histologic chorioamnionitis according to the presence or absence of PROM in group 2. There was no significant difference in the frequency of histologic chorioamnionitis [PROM (+): 16.7 % (7/42) vs PROM (–): 12.2% (19/156), $p>0.1$].

After logistic regression analysis adjusting for potential confounding factors (parity, gestational age at delivery, total duration of labor, duration from rupture of membranes to delivery and mode of delivery), the difference in the frequency of histologic chorioamnionitis between groups 1 and 2 remained significant (Table 3).

DISCUSSION

Principal findings of the study

1) The frequency of histologic chorioamnionitis was different according to the type of onset of labor (spontaneous versus induced). This difference remained significant after adjusting for potential confounding variables, including duration of active labor and rupture of membranes; and 2) the choriodecidua was the most frequent site of inflammation.

Does inflammation precede labor?

A causal link has been established between infection/inflammation and a subgroup of patients with preterm labor and preterm PROM [9]. These patients with intrauterine infection have histologic evidence of inflammation, which is readily diagnosed by examining the extra placental membranes. The infiltration of neutrophils into the chorioamniotic membranes is a maternal host response, indicative of histologic chorioamnionitis.

Inflammation has also been proposed to participate in the mechanisms of spontaneous parturition at term [3, 10–15]. The basis for this concept is that spontaneous labor is associated with a molecular signature of inflammation of the chorioamniotic membranes, myometrium and cervix, which has been established with the use of microarray experiments. Such experiments were designed to examine differential gene expression (transcriptional profiles) of the chorioamniotic membranes between patients not in labor and those in spontaneous labor at term [12]. The data in the current study shows that histologic chorioamnionitis is more frequent in women with spontaneous labor at term than in women who underwent induction of labor, supporting the association between spontaneous

parturition and inflammatory process. The inflammatory process of the components of the common pathway of parturition (myometrium, cervix and chorioamniotic membranes) may be a result of activation of physiologic signals in spontaneous parturition at term.

In contrast, such inflammatory process would be the result of pathologic signals such as infection in a subset of women with spontaneous preterm birth.

Strengths and weaknesses of this study

Few studies have compared the frequency of histologic chorioamnionitis between patients with spontaneous labor and those with induced labor at term: two studies reported no difference in the frequency of chorioamnionitis [16, 17]; however, in one study fever and other signs of clinical chorioamnionitis (not histologic chorioamnionitis) were used to define chorioamnionitis [17]. This is a serious shortcoming because clinical chorioamnionitis is only present in 19–24 % of women with a positive amniotic fluid culture and intact membranes in the context of preterm labor with intact membranes [18–20]. Moreover, a previous study conducted by our group suggests that the prevalence of microbial invasion of the amniotic cavity in women with spontaneous labor at term was 16% [4]. However, most women did not have any evidence of clinical chorioamnionitis.

The other report that addressed the same issue included only births of neonates who were small for gestational age without any definition of chorioamnionitis. In addition, the methods for induction of labor were different in that cervical ripening using a Foley catheter and other mechanical procedures were used [16].

Recently, it has been reported that histologic chorioamnionitis is associated with microbial invasion of amniotic cavity (MIAC) and intra-amniotic inflammation at term[21]. In addition, the presence, progress and duration of labor are associated with increased risk of MIAC, intra-amniotic inflammation, and histologic chorioamnionitis[4, 22]. However, these studies did not issue the type of labor onset (spontaneous versus induced labor) [4, 21, 22].

Unanswered questions and proposal for future research

Histologic chorioamnionitis may result from inflammation or infection. However, microbiologic studies or cytokine analysis of material from gestational tissues or the fetus were not performed in this study. Further investigation incorporating placental pathology, microbiologic studies, and characterization of the pro-inflammatory and anti-inflammatory cytokine profile are needed to evaluate the clinical significance of histologic chorioamnionitis in spontaneous labor at term. Recent evidence suggests that the presence of maternal fever or histologic chorioamnionitis in patients who delivered infants with a birth weight >2500g is associated with an odds ratio of 9 for cerebral palsy [23]. Therefore, the presence of this lesion may have important implications for the newborn as it implies exposure to microbial products before birth.

In conclusion, the frequency of histologic chorioamnionitis at term is more frequent in women with spontaneous onset of labor than in those with induced labor. It is impossible to determine what fraction of acute inflammatory lesions were present at the onset of spontaneous labor at term, and what fraction was acquired during the course of spontaneous

labor. These issues have great biological relevance for the understanding of one of the most important and frequent lesions of the extra-placental membranes: histologic chorioamnionitis.

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Table 1.

Clinical characteristics of the mothers and neonates according to whether labor began spontaneously

	Group 1 (Spontaneous labor, n=333)	Group 2 (Induced labor, n=198)	p value
Clinical characteristics			
Maternal age(yr)	30.9±3.5	31.5±3.4	NS
Gestational age at delivery(wk)	39.7±1.0	40.0±1.2	<0.05
Nulliparity	183/333 (55.0%)	133/198 (67.2%)	< 0.05 [†]
Labor duration (min)	260.0±193.1	243.4±176.7	NS
ROM duration (min)	243.3±414.5	518.6±749.9	< 0.001
Cesarean delivery	27/333 (8.1%)	33/198 (16.7%)	< 0.05 [†]
Maternal fever ^a	50/329 (15.2%)	43/198 (21.7%)	0.06 [†]
Neonatal characteristics			
Birth weight (gm)	3240.8±411.1	3298.7±475.6	NS
SGA	28/333 (8.4%)	23/198 (11.6%)	NS [†]
AS1 < 4	1/333 (0.3%)	5/198 (2.5%)	< 0.05 [*]
AS5 < 7	1/333 (0.3%)	5/198 (2.5%)	< 0.05 [*]
Cord pH	7.285±0.058	7.262±0.069	< 0.001
Meconium staining	73/333 (21.9%)	38/198 (19.2%)	NS [†]
Admission to NICU (adjusted ^a)	2/333 (0.6%)	2/198 (1.0%)	NS [*]

Values are given as mean ± SD.

ROM: rupture of membranes, SGA: small for gestational age, AS1: 1 minute Apgar score, AS5: 5 minute Apgar score, NICU: neonatal intensive care unit, NS: not significant.

^aHighest body temperature of more than 38.0°C on the day of delivery^bNICU admission due to major anomalies were excluded.^{*}Fisher's exact test.[†]Chi-square test

Table 2.

Frequency, site and severity of histologic chorioamnionitis and funisitis in each group

	Group 1 (Spontaneous labor, n=333)	Group 2 (Induced labor, n=198)	p value
Histologic chorioamnionitis	81/333 (24.3%)	26/198 (13.1%)	<0.005
Site of inflammation			
Amnion	17/333 (5.1%)	4/198 (2.0%)	NS [*]
Mild	10/333 (3.0%)	3/198 (1.5%)	
Severe	7/333 (2.1%)	1/198 (0.5%)	
Choriodecidua	81/333 (24.3%)	26/198 (13.1%)	<0.005 [†]
Mild	59/333 (17.7%)	21/198 (10.6%)	
Severe	22/333 (6.6%)	5/198 (2.5%)	
Chorionic plate	11/333 (3.3%)	4/198 (2.0%)	NS [*]
Mild	6/333 (1.8%)	1/198 (0.5%)	
Severe	5/333 (1.5%)	3/198 (1.5%)	
Funisitis	22/333 (6.6%)	12/198 (6.1%)	NS [†]
Mild	12/333 (3.6%)	7/198 (3.5%)	
Severe	10/333 (3.0%)	5/198 (2.5%)	

NS : not significant

^{*} Fisher's exact test.[†] Chi-square test.

The inflammation of amnion and chorio-decidua was defined as the presence of at least one focus of more than 5 neutrophils and considered as severe inflammation if there is diffuse neutrophil infiltration. The inflammation of the chorionic plate was defined as the presence of at least one focus of 10 or more neutrophil foci or diffuse inflammation in the subchorionic fibrin, and considered as severe inflammation if there was diffuse and dense infiltration of neutrophils into the connective tissue of the chorionic plate, or placental vasculitis. Funisitis was defined as neutrophil infiltration confined to umbilical vessel walls and considered as severe funisitis if there was extensive neutrophil infiltration into Wharton's jelly. Mild inflammation was defined when the inflammation did not meet the criteria of severe inflammation.

Table 3.

Logistic regression analysis of significant variables in predicting histologic chorioamnionitis

Variables	Adjusted OR	95% CI		p value
		Lower	Upper	
Spontaneous labor ^a	3.251	1.808	5.844	< 0.001
Cesarean delivery ^b	2.888	1.356	6.148	< 0.05
Gestational age at delivery	1.367	1.069	1.747	< 0.05
Labor duration	1.003	1.001	1.004	< 0.001
Nulliparity	1.374	0.783	2.409	NS
ROM duration	1.000	1.000	1.001	NS

ROM : rupture of membranes, NS : not significant.

Reference:

^a induced labor^b vaginal delivery