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The Frequency and Clinical Significance of Intra-amniotic Inflammation in Women With Preterm Uterine Contractility but Without Cervical Change: Do the Diagnostic Criteria for Preterm Labor Need to be Changed?

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Abstract

OBJECTIVE—The objective of this study was to determine the frequency and clinical significance of intra-amniotic inflammation in patients with preterm increased uterine contractility with intact membranes but without cervical change.

METHODS—Amniocentesis was performed in 132 patients with regular uterine contractions and intact membranes without cervical change. Amniotic fluid was cultured for bacteria and mycoplasmas and assayed for matrix metalloproteinase-8 (MMP-8). Intra-amniotic inflammation was defined as an elevated amniotic fluid MMP-8 concentration (>23 ng/mL).

RESULTS—1) Intra-amniotic inflammation was present in 12.1% (16/132); 2) Culture-proven intra-amniotic infection was diagnosed in 3% (4/132) of patients without demonstrable cervical change on admission or during the period of observation; and 3) Patients with intra-amniotic inflammation had significantly higher rates of preterm delivery and adverse outcomes, and shorter amniocentesis-to-delivery intervals than those without intra-amniotic inflammation ($P < .05$ for each). Adverse outcomes included chorioamnionitis, funisitis, and neonatal death.

CONCLUSION—Intra-amniotic inflammation was present in 12% of patients with regular uterine contractions without cervical change, while culture-proven intra-amniotic infection was present in 3%. The presence of intra-amniotic inflammation was a significant risk factor for adverse neonatal outcomes. These observations question whether cervical changes should be required for the diagnosis of preterm labor, because patients without modifications in cervical status on admission or during a period of observation are at risk for adverse pregnancy outcomes.

Keywords

prematurity; preterm parturition; preterm birth; prognosis; preterm delivery; micro-organisms; matrix metalloproteinase; MMP8; funisitis; histologic chorioamnionitis

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Declaration of interest All authors declare no conflicts of interest.

Introduction

The diagnosis of labor (both term and preterm) is a major challenge in obstetrics [1-6]. The standard view is that a certain diagnosis of labor can only be made retrospectively once increased uterine contractility leads to progressive cervical dilatation and impending or actual delivery [2].

The differential diagnosis between “true” spontaneous labor at term and “false labor” continues to be a dilemma. Virtually every labor and delivery unit has had the experience of having discharged a patient with the diagnosis of false labor and then learning that the patient delivered on her way back to the hospital. In most instances, this does not represent a problem because term neonates are mature and experience few complications.

On the other hand, a “false negative” diagnosis of preterm labor can have more serious implications [7-10]. Patients often present to the hospital with increased uterine contractility, and obstetricians are expected to identify those who have Braxton-Hicks contractions from those who are in “true” preterm labor. However, there is no “gold standard” to diagnose “true” preterm labor. Some physicians have introduced the term “threatened preterm labor” to describe the clinical condition in which a patient has increased uterine contractility with or without cervical changes.

The standard criteria for the diagnosis of preterm labor recommended by professional organizations and investigators have changed over time. Decades ago, preterm labor was suspected purely on the basis of increased uterine contractility; however, when the concept of tocolysis was introduced into obstetrics, the use of pharmacologic agents (e.g. intravenous alcohol or non-specific adrenergic agents) administered to achieve uterine relaxation was associated with serious adverse events which could be lethal to the mother [11-13]. Thus, the need emerged to identify patients who were at greater risk for preterm delivery in whom tocolysis “should” be used. This is how a change in cervical status (e.g. progressive cervical change or cervical changes at the time of diagnosis) became part of the standard criteria to diagnose preterm labor [14,15]. Patients with such diagnosis would be eligible for the administration of tocolysis and steroids, while those without cervical change are monitored and often discharged. Yet, these patients are at increased risk for preterm delivery [16-23].

To address the question of whether patients with an increase in uterine contractility but without cervical change could have serious pathologic processes, we investigated the frequency of intra-amniotic infection/inflammation and its clinical significance. The basis for this is that intra-amniotic infection/inflammation is a risk factor for adverse pregnancy outcome and neonatal morbidity [24-75].

Materials and Methods

Study population

The study population consisted of consecutive patients who were admitted to Seoul National University Hospital, Seoul, Republic of Korea, with regular uterine contractions and intact membranes without cervical change before 35 weeks of gestation. The patients met the following criteria: (1) singleton gestation; (2) regular uterine contractions - eight or more in 60 minutes; (3) initial cervical dilatation ≤ 1 cm and effacement ≤ 75% by digital cervical examination and no cervical change for at least 3 hours; and (4) transabdominal amniocentesis for microbiologic studies or assessment of fetal lung maturity. Patients with placenta previa or those who had previously undergone a cervical cerclage were excluded.

The Institutional Review Board of Seoul National University Hospital, Seoul, Republic of Korea, has approved the collection and utilization of the biological materials and clinical data for research purposes.

Amniotic fluid

Amniotic fluid was obtained by transabdominal amniocentesis with ultrasound guide and aseptic technique with written informed consent. Amniotic fluid was cultured for aerobic and anaerobic bacteria, as well as for genital mycoplasmas (ureaplasmas [*Ureaplasma urealyticum* & *Ureaplasma parvum*] and *Mycoplasma hominis*), and used for assessment of fetal lung maturity. The remaining amniotic fluid was centrifuged, and the supernatant was stored at −70°C until assayed.

Intra-amniotic inflammation was defined as an elevated amniotic fluid matrix metalloproteinase-8 (MMP-8) concentration (>23 ng/mL), as previously reported [76]. Previous studies indicated that amniotic fluid MMP-8 is a sensitive and specific index of intra-amniotic inflammation and correlates with an amniotic fluid white blood cell (WBC) count [77,78]. MMP-8 concentration in the stored amniotic fluid was measured with a commercially available, enzyme-linked immunosorbent assay (Amersham Pharmacia Biotech, Inc., Little Chalfont, Buckinghamshire, UK) with a sensitivity of 0.3 ng/mL. Both inter- and intra- assay coefficients of variation were < 10%.

Acute histologic chorioamnionitis, funisitis and neonatal morbidity

Clinical chorioamnionitis was diagnosed according to definitions previously described in detail [79]. Acute histologic chorioamnionitis was diagnosed when inflammatory change was detected in any part of the placental tissue samples (amnion, chorion-decidua and chorionic plate); funisitis was diagnosed in the presence of neutrophil infiltration into the umbilical vessel walls or into Wharton's jelly, according to the criteria previously reported [80]. Significant neonatal morbidity was defined when any of the following conditions was diagnosed: proven congenital neonatal sepsis, respiratory distress syndrome, congenital pneumonia, bronchopulmonary dysplasia, intraventricular hemorrhage (grade ≥II), and necrotizing enterocolitis. The diagnostic criteria of each condition were described in detail in previous reports from our group [81].

Statistical analysis

Comparison of the continuous variables was performed by using the Mann-Whitney *U* test. Proportions were compared with the Pearson Chi-Square or Fisher's exact tests. Logistic regression analysis was used to examine the relationship between the presence of intra-amniotic inflammation and adverse perinatal outcomes of interest to adjust for potential confounding factors. Survival analysis was used to compare the amniocentesis-to-delivery interval according to the presence or absence of intra-amniotic inflammation. Patients delivered for maternal or fetal indications were treated as censored observations, with a censoring time equal to the amniocentesis-to-delivery interval. The Cox proportional hazards model was used to control covariates and to investigate the hazards ratio. A probability value of < .05 was considered to be of statistical significance.

Results

The frequency of intra-amniotic infection and inflammation

Intra-amniotic inflammation was present in 12.1% (16/132) of the patients with regular uterine contractions without cervical change, and microorganisms were detected in 3.1% of these cases (4/130). Microorganisms isolated from amniotic fluid were *Ureaplasma urealyticum* (n=2), *Mycoplasma hominis* and *Streptococcus anginosus* (n=1; one patient had

2 organisms), and *Acinetobacter Bauman* (n=1). All patients with a positive amniotic fluid culture had intra-amniotic inflammation. On the other hand, 13 patients with intra-amniotic inflammation had negative amniotic fluid cultures.

Characteristics of study population

Table I shows the clinical characteristics of the study population according to the presence or absence of intra-amniotic inflammation. Patients with intra-amniotic inflammation had a significantly lower median gestational age at amniocentesis than those without inflammation ($P < .05$). There were no significant differences in maternal age, parity, interval from admission to amniocentesis, frequency of uterine contractility and the rate of administration of tocolysis between patients with and without intra-amniotic inflammation ($P > .1$, Table I).

Amniocentesis-to-delivery interval

Patients with intra-amniotic inflammation had significantly shorter amniocentesis-to-delivery intervals than those without intra-amniotic inflammation as demonstrated by survival analysis ($P = .001$; Figure 1), and intra-amniotic inflammation was significantly associated with a short interval to delivery after the adjustment for gestational age (hazards ratio, 6.9; 95% CI, 3.7-12.5; $P < .05$, Cox proportional hazards model analysis).

Pregnancy outcome

Table II demonstrates pregnancy and neonatal outcomes of the study population according to the presence or absence of intra-amniotic inflammation. Patients with intra-amniotic inflammation had significantly lower median gestational ages at birth and birthweights, and higher rates of preterm delivery, histologic chorioamnionitis, funisitis, neonatal death, and admissions to the neonatal intensive care unit than those without intra-amniotic inflammation ($P < .05$ for each, Table II).

Subgroup analysis according to the duration of observation of cervical change

The current study included patients with regular uterine contractions and no cervical change for at least 3 hours. We also included patients with no cervical change for at least 6 hours. In such patients, the rate of intra-amniotic inflammation was 13.6% (11/81). Table III compares the outcome between patients with and without intra-amniotic inflammation in patients with regular uterine contractions and no cervical change for 6 hours or more. Patients with intra-amniotic inflammation had significantly higher rates of adverse outcomes than those without inflammation ($P < .05$ for each). Patients with intra-amniotic infection had significantly lower gestational ages at birth and birthweights. They also had shorter amniocentesis-to-delivery intervals and higher rates of preterm delivery, histologic chorioamnionitis, funisitis, neonatal death and admissions to the neonatal intensive care unit.

We also analyzed our data to focus on patients who did not have cervical change for at least 12 hours. Intra-amniotic inflammation was found in 12.5% (6/48). Similarly, patients with intra-amniotic inflammation had significantly lower median gestational ages at birth, lower median birthweights, shorter median intervals to delivery, and higher rates of preterm delivery, histologic chorioamnionitis, funisitis, and neonatal death than those without inflammation in patients with regular uterine contractions and no cervical change for at least 12 hours ($P < .05$ for each).

Comment

Principal findings of the study

1) Patients with increased preterm uterine contractility and intact membranes but without cervical change have a prevalence of intra-amniotic inflammation of 12% and culture-proven intra-amniotic infection of 3%. The organisms found in the amniotic cavity are similar to those involved in intra-amniotic infection in preterm labor with intact membranes [82-87] or preterm prelabor rupture of membranes [88-94]; 2) patients with intra-amniotic inflammation were at risk for preterm delivery and adverse neonatal outcome as well as histologic chorioamnionitis and funisitis; 3) these data indicate that a fraction of patients who do not meet the clinical definition of preterm labor as currently recommended by textbooks and professional organizations are still at risk for preterm delivery, intra-amniotic infection/inflammation, and adverse pregnancy outcome; and 4) preterm labor and delivery can occur in patients without cervical change at presentation or within a 12-hour period of observation.

Intra-amniotic infection/inflammation in patients with preterm labor and intact membranes and without cervical change

This is the first and only study which focused exclusively on this population and, therefore, our findings cannot be compared with other reports. However, the presence of microbial invasion of the amniotic cavity with bacteria has been demonstrated in patients at term not in labor [95,96], undergoing mid-trimester amniocentesis [97-99], those with an asymptomatic short cervix [100-104] and those with idiopathic vaginal bleeding [105]. Patients in the latter two categories have an excess of intra-amniotic infection/inflammation over those who are at term not in labor or who undergo mid-trimester amniocentesis for genetic indications. Such observations suggest that subclinical intra-amniotic infection/inflammation may lead to either a short cervix or vaginal bleeding.

Table IV displays the prevalence of microbial invasion observed in different obstetrical syndromes [86,101,106-192]. It is noteworthy that, among patients with preterm labor and intact membranes, the mean frequency of microbial invasion at the time of admission is approximately 12%. This is four-fold higher than that observed in patients with preterm labor and intact membranes in the current study, and our observations confirm previous findings that the more advanced the cervical dilatation or the shorter the cervix in ultrasound examinations, the higher the frequency of intra-amniotic infection/inflammation [101,193-197].

We have previously demonstrated a similar prognosis for patients with intra-amniotic inflammation and a negative amniotic fluid culture and for those with culture-proven intra-amniotic infection [198-200]. Therefore, the finding reported herein that 12% of patients with increased preterm uterine contractility have intra-amniotic inflammation and adverse outcome is of importance because this is the most common presentation of patients suspected to have preterm labor.

The cause of intra-amniotic inflammation in patients with negative amniotic fluid cultures can be bacterial infection that escaped detection with cultivation techniques [201,202] or viral infection [203-205]. We have previously demonstrated that molecular microbiologic techniques are able to identify microbial footprints in patients with intra-amniotic inflammation but negative amniotic fluid cultures [86,206-209]. It is possible that, if such techniques were used, the rate of intra-amniotic infection would be higher. The same applies for techniques to isolate the presence of viruses.

The common pathway of parturition

We have proposed that the common pathway of parturition [210,211] involves: 1) increased uterine contractility; 2) cervical ripening; and 3) membrane/decidual activation. These components can be activated in a synchronous manner and then the patient with overt activation of the three components will present with increased uterine contractility, cervical dilatation, and membrane rupture. Subclinical degrees of activation can occur which can only be detected with surface electromyography [212-214], cervical ultrasound [101,215-217], coloscope, or the presence of extracellular matrix proteins, such as fibronectin in cervico-vaginal fluid, for membrane decidual activation [218-223].

Asynchronous activation of the common pathway can also occur. Hence, the patient can present with isolated increased uterine contractility, isolated cervical insufficiency, [224,225] or preterm prelabor rupture of membranes [226,227]. Patients with less overt signs of asynchronous activation of the common pathway are also observed. Typically, such patients were the subjects of the present study. However, the greater the number of components of the common pathway that are activated, the more likely the patient will have preterm labor that will lead to preterm delivery.

Requirement of cervical change for the diagnosis of preterm labor

The requirement for some degree of change in cervical status for the diagnosis of preterm labor was introduced in clinical practice to minimize the number of patients who would be treated with tocolytic agents [228,229]. The primary rationale behind the requirement of changes in cervical status for the diagnosis of preterm labor was the avoidance of overtreatment and prevention of adverse events. It was reasoned that if the patient with isolated preterm uterine contractions would continue to have contractions and the cervix changed, this would be diagnostic of preterm labor and that such patient would still be in time for treatment to arrest uterine contractility with tocolysis and for the prevention of preterm delivery.

Many patients admitted to a labor and delivery unit with the suspicion of preterm labor are given intravenous hydration. Pircon et al. [230] reported the outcome of 48 patients with preterm uterine contractions but without cervical change randomized to bed rest (n=28) or bed rest and hydration (n=20). Twenty-two patients stopped contracting; however, 18% (4/22) subsequently delivered preterm neonates. Therefore, whatever the apparent short-term clinical response to hydration might be, patients remain at risk for preterm delivery. This has also been the case when patients have been randomized to receive a single injection of subcutaneous terbutaline. Even though contractions are likely to abate, pregnancy outcome is no different in patients who receive terbutaline than in the control group [231,232]. Collectively, these studies highlight the clinical difficulties of the diagnosis of preterm labor and that attempts to implement interventions in the hope that they would assist in the differential diagnosis between true and false preterm labor have not been successful.

Clinical implications of this study

Our observations suggest that patients presenting with an episode of increased preterm uterine contractility without cervical changes cannot be considered to have false preterm labor and to be risk-free. Although many clinicians discharge such patients from the labor and delivery unit, not only do they remain at risk for preterm delivery, but a fraction has intra-amniotic infection/inflammation and the increased frequency of uterine contractions may be the only sign of that pathologic process. For these reasons, we propose that the diagnosis of intra-amniotic infection/inflammation be undertaken, and that management be changed if that is the case (administration of antibiotics and steroids, and suspension of tocolysis if initiated) [101,233-235]. Patients can be counseled that those with intra-amniotic

inflammation will deliver a preterm neonate in 87.5% of cases (see Table II). The absence of intra-amniotic inflammation reduces the risk of preterm delivery (32.8%; see Table II), and the pathologic mechanisms responsible for this have not been elucidated but may be related to chronic chorioamnionitis, which is evidence of maternal anti-fetal rejection [236,237].

Cervical change during the period of observation

Textbooks and investigators recommend that the diagnosis of preterm labor be made if cervical changes are present at admission, and if such changes are documented during a period of observation. However, the precise duration of the period of observation and the miminum change required to make a diagnosis are rarely specified – even when they are, the scientific basis for this is unclear. It is noteworthy that, in the current study, the frequency of intra-amniotic infection/inflammation was no different if the patients presented without cervical change on admission, or if the cervix did not change after 12 hours.

Why would some patients with increased preterm uterine contractility but without cervical change have intra-amniotic infection/inflammation?

One possibility is that patients have an intra-amniotic infection of hematogenous origin. Indeed, we and others have found bacteria in amniotic fluid which are normally found in the oral cavity using molecular techniques [238,239]. This suggests that some patients may have a bacteremia, and the transplacental passage of the bacteria causes intra-amniotic infection. Another possibility is that the uterine cavity (decidua) is not sterile during pregnancy, and bacteria are present in biofilms which do not elicit a robust proinflammatory host response. However, fracture of the biofilm may result in the release of planktonic bacteria, which would be capable of multiplication, passage across the membranes, and the induction of inflammation. We have previously reported that patients who have bacteria in the chorioamniotic space have a higher mean amniotic fluid IL-6 concentration than those without bacteria in the chorioamniotic space [240]. IL-6 is a reliable marker of intra-amniotic inflammation.

A possibility that should not be overlooked is that if the mucus plug is lost or defective [241-244], microorganisms from the lower genital tract may ascend into the uterus during uterine contractions. Indeed, a recent study indicated that vaginal fluid can ascend into the uterine cavity by a suction-like effect caused by uterine contractions (demonstrated byhystero-salpingo scintigraphy with contrast media) [245]. Therefore, it is possible that uterine contractions in the appropriate host (one in which the innate immune system is compromised because of a defective mucus plug or the loss of the mucus plug in patients with a short cervix) may predispose to ascending intra-amniotic infection/inflammation.

It is noteworthy that 19% of patients with spontaneous labor at term with intact membranes have a positive amniotic fluid culture [246]. These observations have been confirmed by studying the microbial state of the amniotic cavity in patients in spontaneous labor at term undergoing cesarean section [247].

CONCLUSION

This study shows that subclinical intra-amniotic infection/inflammation is present in a fraction of patients with an episode of preterm labor with intact membranes and without cervical change. Thus, preterm uterine contractions may be the only clinical manifestation of intra-amniotic inflammation. However, an important implication of our observation is that preterm labor leading to preterm delivery can present itself as increased preterm uterine contractility without cervical change. This observation calls for a re-examination of the diagnostic criteria for preterm labor.

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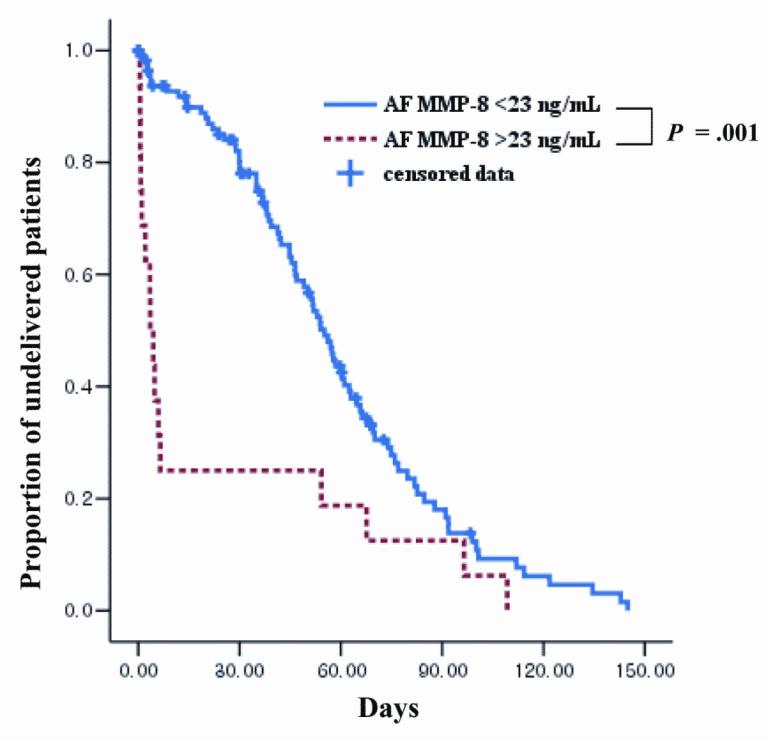

Figure 1. Survival analysis of amniocentesis-to-delivery interval

Patients with intra-amniotic inflammation had a significantly shorter amniocentesis-to-delivery interval than those without inflammation (median, 4.0 days [range, 0.5-109.3 days] vs. median, 45.9 days [range, 0.0-144.9 days]; log rank, *P*= .001).

Table I

Clinical characteristics according to the presence or absence of intra-amniotic inflammation

	Intra-amniotic inflammation		*P* value
	Negative[a] (n=116)	Positive[b] (n=16)	
Maternal age (y)[c]	30.0 (23-42)	29.5 (25-43)	NS
Nulliparity (n)	68 (58.6%)	11 (68.8%)	NS
Gestational age at amniocentesis (wk) [c]	31.6 (19.0-34.9)	28.5 (20.9-34.6)	< .05
Interval to amniocentesis from admission (hr) [c]	8.0 (3.0-336.0)	8.0 (3.0-272.0)	NS
No. of uterine contraction (/hr) [d]	17.7 ± 8.7	15.4 ± 5.1	NS
Tocolysis at amniocentesis (n)	74 (63.8%)	12 (75.0%)	NS

AF, amniotic fluid; *MMP-8*, matrix metalloproteinase-8; *NS*, not significant.

[a]Negative, AF MMP-8 < 23 ng/mL

[b]Positive, AF MMP-8 > 23 ng/mL

[c]Values are given as median (range)

[d]Data given as mean ± SD

Table II

Pregnancy and neonatal outcome according to the presence or absence of intra-amniotic inflammation

	Intra-amniotic inflammation		*P* value	
	Negative[a] (n=116)	Positive[b] (n=16)	*Unadjusted*	*Adjusted* [c]
Gestational age at delivery (wk)[d]	38.4 (21.4-42.6)	32.7 (21.4-38.3)	<.001	–
Amniocentesis-to-delivery interval (n)				
≤48 hr	7 (6.0%)	5 (31.3%)	< .01	< .01
≤7 d	15 (12.9%)	12 (75.0%)	< .001	< .001
Preterm delivery (n)	38 (32.8%)	14 (87.5%)	<.001	< .001
Clinical chorioamnionitis (n)	0 (0.0%)	3 (18.8%)	< .01	–
Histologic chorioamnionitis (n/N)[e,f]	15/66 (22.7%)	7/10 (70.0%)	< .01	< .01
Funisitis (n/N)[e,f]	2/66 (3.0%)	5/10 (50.0%)	< .001	< .001
Birthweight (g)[d]	2930 (390-4200)	1865 (550-2810)	< .001	–
1-minute Apgar score <4 (n/N) [f]	7/92 (7.6%)	4/14 (28.6%)	< .05	.054
5-minute Apgar score <7 (n/N) [f]	5/92 (5.4%)	4/14 (28.6%)	< .05	< .05
Neonatal deaths (n/N) [g]	2/112 (1.8%)	4/16 (25.0%)	< .01	< .01
Shortly after birth,<1 day	1	4		
Perinatal period,<1 month	1	0		
Admission to NICU (n/N)[f,h]	18/92 (19.6%)	7/11 (63.6%)	< .01	< .01
Significant neonatal morbidity (n/N)[f,h]	9/92 (9.8%)	3/11 (27.3%)	NS	NS
Neonatal mortality and significant morbidity (n/N)	10/93 (10.8%)	7/15 (46.7%)	< .01	< .01

AF, amniotic fluid; *MMP-8*, matrix metalloproteinase-8; *NS*, not significant; *NICU*, neonatal intensive care unit.

[a] Negative, AF MMP-8 < 23 ng/mL.

[b] Positive, AF MMP-8 > 23 ng/mL.

[c] Adjusted for gestational age at amniocentesis (logistic regression analysis).

[d] Values are given as median (range).

[e] Cases without placental examination were excluded.

[f] Cases delivered at other hospitals were excluded, most of them were delivered at term without complication.

[g] Cases with major anomaly were excluded.

[h] Cases with major anomaly or died in the delivery room were excluded. Significant neonatal morbidity was defined as the presence of any following conditions: proven neonatal sepsis, respiratory distress syndrome, pneumonia, bronchopulmonary dysplasia, intraventricular hemorrhage (grade ≥ II), and necrotizing enterocolitis. Five newborns who died within 1 day with or without resuscitation due to extreme prematurity were excluded because they could not be evaluated for morbidity.

Table III

Outcomes in patients with regular uterine contractions and no cervical change for at least 6 hours

	Intra-amniotic inflammation		*P* value	
	Negative[a] (n=70)	**Positive[b] (n=11)**	***Unadjusted***	***Adjusted*** [c]
Gestational age at delivery (wk)[d]	38.4 (21.4-41.6)	32.1 (21.4-38.3)	< .001	–
Amniocentesis-to-delivery interval (n)				
≤48 hr	4 (5.7%)	4 (36.4%)	< .05	< .05
≤7 d	9 (12.9%)	8 (72.7%)	< .001	< .001
Preterm delivery (n)	20 (28.6%)	10 (90.9%)	< .001	< .05
Histologic chorioamnionitis (n/N)[e,f]	7/38 (18.4%)	4/5 (80.0%)	< .05	< .05
Funisitis (n/N)[e,f]	0	2/5 (40.0%)	< .05	–
Birthweight (g)[d]	2970 (390-4200)	1680 (550-2810)	< .001	–
1-minute Apgar score <4 (n/N) [f]	5/55 (9.1%)	4/9 (44.4%)	< .05	< .05
5-minute Apgar score <7 (n/N) [f]	2/55 (3.6%)	4/9 (44.4%)	< .01	< .01
Neonatal deaths (n/N) [g]	1/68 (1.5%)	4/11 (36.4%)	< .01	< .05
Admission to NICU (n/N)[f,h]	9/55 (16.4%)	4/6 (66.7%)	< .05	< .05
Significant neonatal morbidity (n/N)[f,h]	6/55 (10.9%)	2/6 (33.3%)	NS	NS
Neonatal mortality and significant morbidity (n/N)	7/56 (12.5%)	6/10 (60.0%)	< .01	< .05

AF, amniotic fluid; *MMP-8*, matrix metalloproteinase-8; *NS*, not significant; *NICU*, neonatal intensive care unit.

[a] Negative, AF MMP-8 < 23 ng/mL.

[b] Positive, AF MMP-8 > 23 ng/mL.

[c] Adjusted for gestational age at amniocentesis (logistic regression analysis).

[d] Values are given as median (range).

[e] Cases without placental examination were excluded.

[f] Cases delivered at other hospitals were excluded, most of them were delivered at term without complication.

[g] Cases with major anomaly were excluded.

[h] Cases with major anomaly or died in the delivery room were excluded. Significant neonatal morbidity was defined as the presence of any following conditions: proven neonatal sepsis, respiratory distress syndrome, pneumonia, bronchopulmonary dysplasia, intraventricular hemorrhage (grade ≥ II), and necrotizing enterocolitis. Five newborns who died within 1 day with or without resuscitation due to extreme prematurity were excluded because they could not be evaluate about morbidity.

Table IV

Prevalence of microbial invasion reported for the different obstetrical syndromes

Obstetrical syndromes	Microbial invasion in amniotic fluid
Term not in labor [86,87]	1%
Term in labor [86,87,125]	4%-19%
Premature rupture of membranes at term [119]	34%
Premature rupture of membranes at preterm [30,42,58,61,71,75,82,84,96,100,101,103,105,106,117,121,122,126,128,130,131,134,135,143,145,146,150,151,158]	15%-58%
Preterm labor with intact membranes [22-25,28,32,40,75,78-80,97-99,102,104,107-118,121,123,124,127,129,132-134,136-142,144,147,149,159,160]	0%-48%
Cervical insufficiency [72,120,152]	8%-52%
Short cervix [91,94,148]	4%-9%
Small for gestational age [156]	0%
Preeclampsia [155]	2%
Vaginal bleeding [95,153,157]	5%-14%