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CLINICAL SIGNIFICANCE OF OLIGOHYDRAMNIOS IN PATIENTS WITH PRETERM LABOR AND INTACT MEMBRANES

Byoung Jae KIM, MD^{1,2}, Roberto ROMERO, MD³, Seung Mi LEE, MD^{1,4}, Chan-Wook Park, MD, PhD^{1,4}, Joong Shin PARK, MD, PhD^{1,4}, Jong Kwan JUN, MD, PhD^{1,4}, and Bo Hyun YOON, MD, PhD^{1,4}

¹Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, Korea

²Department of Obstetrics and Gynecology, Seoul Metropolitan Government Seoul National University Boramae Medical center, Seoul, Korea

³Perinatology Research Branch, NICHD/NIH/DHHS, Bethesda, MD, and Detroit, MI

⁴Department of Obstetrics and Gynecology, Seoul National University Hospital, Seoul, South Korea

Abstract

OBJECTIVE—To determine the frequency and clinical significance of oligohydramnios in patients with preterm labor and intact membranes.

STUDY DESIGN—An amniotic fluid index (AFI) was determined before amniocentesis (<24hrs) in 272 patients with preterm labor and intact membranes (<35 weeks of gestation). Amniotic fluid (AF) was cultured for aerobic and anaerobic bacteria and genital mycoplasmas, and assayed for matrix metalloproteinase-8 (MMP-8). Nonparametric statistical techniques and survival analysis were used.

RESULTS—1) The overall prevalence of oligohydramnios (AFI of ≤ 5 cm) in patients with preterm labor and intact membranes was 2.6% (7/272); 2) patients with oligohydramnios had a higher frequency of AF infection and/or inflammation than those without oligohydramnios (85.7% [6/7] vs. 32.8% [87/265]; $p < .01$); 3) Patients with oligohydramnios had a higher median AF MMP-8 concentration than those without oligohydramnios (median 664.2 [range 16.6 – 3424.7] ng/ml vs. median 2.3 [range <0.3 – 6142.6] ng/ml; $p < .01$); 4) women with preterm labor and oligohydramnios had a shorter interval to delivery than those without oligohydramnios (median 18 hrs [range 0-74 hrs] vs. median 311 hrs [range 0-3228 hrs]; $p < .01$), and this difference remained significant after adjusting for gestational age and the presence or absence of AF infection/inflammation

CONCLUSION—Patients with preterm labor and oligohydramnios are at increased risk for impending preterm delivery and intra-amniotic inflammation and, therefore, may benefit from careful surveillance.

Correspondence to: Bo Hyun Yoon, MD, PhD, Department of Obstetrics and Gynecology, College of Medicine, Seoul National University, Seoul, 110-744, Korea. Tel: 82-2-2072-2826, Fax: 82-2-765-3002, Yoonbh@snu.ac.kr.

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Keywords

amniocentesis-to-delivery interval; intra-amniotic inflammation; oligohydramnios; prematurity; preterm labor

Introduction

Ultrasound examination is a part of the routine assessment of patients admitted with the diagnosis of preterm labor with intact membranes. The clinical significance of a reduced volume of amniotic fluid (AF) in this specific setting is unknown. Such a finding has prognostic significance in patients with preterm premature rupture of membranes (PROM) [1, 11, 20, 25, 30, 36, 46, 50-51]. The objective of the study was to determine the frequency and clinical significance of oligohydramnios in patients with preterm labor and intact membranes.

Material and methods

Study design

The study population consisted of consecutive patients admitted to Seoul National University Hospital between January 1993 and June 2006 with the diagnosis of preterm labor and intact membranes (<35 weeks of gestation) and singleton gestation who underwent amniocentesis and measurement of amniotic fluid index (AFI) within 24 hours before amniocentesis. Preterm labor was diagnosed as the presence of regular uterine contractions (four or more contractions in 20 minutes or eight or more in 60 minutes). Amniocentesis is routinely offered to all patients who are admitted with the diagnosis of preterm labor at our institution. Amniocentesis was performed after written informed consent was obtained. Intra-amniotic inflammation was defined as an elevated AF MMP-8 concentration (>23 ng/ml) as previously reported [35, 45]. The institutional review board of the participating institution approved the collection of biologic materials and data from these patients for research purposes.

AFI and amniocentesis

The AFI was determined according to the method described by Phelan et al [40]. AF was retrieved by transabdominal amniocentesis and was cultured for aerobic and anaerobic bacteria and genital mycoplasmas (ureaplasmas and *Mycoplasma hominis*). The results of amniotic fluid culture, white blood cell (WBC) count and lung maturity test were used for patient management. For example, in some patients with a positive lung maturity and an increased amniotic fluid WBC count, delivery was performed, and these patients had their amniocentesis-to-delivery interval treated as a censored observation and survival technique was used for the analysis. Fluid that was not used for diagnostic studies was centrifuged and stored at -70°C until assayed. MMP-8 concentrations were measured with a commercially available enzyme-linked immunosorbent assay (Amersham Pharmacia Biotech, Inc, Bucks, UK). The sensitivity of the test was 0.3 ng/mL. Intra- and interassay coefficients of variation were 3.1% and 9.5%, respectively.

Diagnosis of chorioamnionitis and small for gestational age (SGA) infant

Clinical chorioamnionitis was defined according to the criteria proposed by Gibbs et al [9]. The diagnosis required a temperature elevation to 37.8°C and two or more of the following criteria: uterine tenderness, malodorous vaginal discharge, maternal tachycardia, fetal tachycardia, and leukocytosis. Leukocytosis was defined as a white blood cell count

$>15,000/\text{mm}^3$. Histologic chorioamnionitis was defined as the presence of acute inflammatory changes in any tissue samples (amnion, choriondecidua, umbilical cord, and chorionic plate) of extraplacental membranes [55]. Small for gestational age (SGA) infants were classified as those whose weights were below the 10th percentile for their gestational age [37].

Statistical analysis

Univariate analysis was performed with the Mann-Whitney *U* test, the student *t* test, or the Fisher's exact test. The amniocentesis-to-delivery intervals were compared by generalized Wilcoxon test for survival analysis. Patients delivered for maternal or fetal indications were treated as censored observations, with a censoring time equal to the amniocentesis-to-delivery interval. Cox proportional hazards model analysis was used to examine the relationship between AFI and amniocentesis interval after the adjustment for covariates.

Results

Amniocentesis was performed in 311 patients with preterm labor and intact membranes during the study period. Thirty seven patients with no available amniotic fluid index (AFI) within 24 hours before amniocentesis were excluded. Two patients with negative AF cultures and no available AF for MMP-8 determination were excluded from the further analysis, because they could not be evaluated with respect to the presence or absence of intra-amniotic inflammation. Two hundred seventy-two patients were eligible for study.

The prevalence of oligohydramnios (AFI of ≤ 5 cm) was 2.6% (7/272). The prevalence of positive AF culture was 8.1% (22/272). Three patients had polymicrobial infections with 2 species of micro-organisms and *Ureaplasma urealyticum* was isolated in two of them. Microorganisms isolated from the AF included *Ureaplasma urealyticum* (n=10), *Lactobacillus* species (n=2), *Acinetobacter* species (n=2), *Streptococcus anginosus* (n=2), and one isolate each of *Candida* species, *Porphyromonas*, *Staphylococcus aureus*, *Enterococcus faecium*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Mycoplasma hominis*, and *Streptococcus viridans*. The AF MMP-8 concentration of the patient with a positive AF culture for *Staphylococcus aureus*, which is commonly considered as a skin contaminant, was 142.6 ng/ml.

Table 1 compares the clinical characteristics and outcomes of the study population according to the AFI. The frequency of intra-amniotic inflammation was higher in patients with an AFI of ≤ 5 cm than those with an AFI of >5 cm (86% [6/7] vs. 30% [80/265]; $p<.01$). Patients with oligohydramnios had a significantly higher median AF MMP-8 (median 664.2 [range 16.6 – 3424.7] ng/ml vs. median 2.3 [range <0.3 – 6142.6] ng/ml; $p<.01$, Figure 1) and a lower median gestational age at birth and mean birth weight than those without oligohydramnios. There were no significant differences in the median gestational age at amniocentesis and rates of SGA, umbilical artery cord blood pH <7.15 and Apgar score <7 (1-min and 5-min) between the two groups of patients ($p>.1$).

Women with preterm labor and oligohydramnios had a shorter interval to delivery than those without oligohydramnios (amniocentesis-to-delivery interval: median, 18 hrs [range 0-74 hrs] vs. median, 311 hrs [range 0-3228 hrs]; $p<.01$, Figure 2). Thirty six patients were delivered for maternal or fetal indications [term/near term or fetal lung maturation (n=17), preeclampsia (n=3), maternal disease (n=3), suspicious fetal distress (n=5), vaginal bleeding (n=5), and others (n=3)]; these patients were treated as censored observations, with a censoring time equal to the amniocentesis-to-delivery interval. Multivariate survival analysis indicated that oligohydramnios was an independent predictor of the duration of the

pregnancy after adjusting for gestational age and the presence or absence of AF infection and/or intra-amniotic inflammation (hazards ratio, 2.7; 95% confidence interval, 1.2-5.8).

Table 2 shows the characteristics of the seven cases with oligohydramnios. Spontaneous or artificial ROM was subsequently confirmed after the ultrasonography/amniocentesis during hospital course in all 4 cases that were delivered vaginally.

Discussion

Principal findings of this study

1) The frequency of oligohydramnios (AFI $\leq$ 5 cm) was 2.6% (7/272) among patients who had preterm labor and intact membranes; and 2) patients with a reduced volume of AF had a higher frequency of intra-amniotic inflammation and a shorter amniocentesis-to-delivery interval than those with an AFI of >5 cm.

Previous observations about the clinical significance of a reduced volume of AF in patients at risk for preterm delivery

The findings described herein are consistent with those previously reported in patients with preterm PROM in which oligohydramnios was found to be a risk factor for proven AF infection, intra-amniotic inflammation, and a short amniocentesis-to-delivery interval [11, 20, 25, 30, 36, 46, 50-51]. Moreover, patients with a reduced AF volume had a higher AF concentration of interleukin-6, tumor necrosis factor alpha and interleukin-1 beta than those with an AFI of > 5 cm [54]. In addition, the umbilical cord concentrations of interleukin-6 were higher in patients with a reduced volume of AF than in those without oligohydramnios [54].

Why is a reduced volume of AF associated with intra-amniotic inflammation and a short interval to delivery?

AF has antimicrobial properties [3, 8, 17, 44] and this may be part of the innate immune system. A reduced volume of AF may decrease the natural host defense conferred by this fluid and predispose toward intrauterine infection. Alternatively, intra-amniotic inflammation may lead to oligohydramnios. In the case of preterm PROM, we have proposed that microbial invasion of the amniotic cavity, fetal infection and the development of the fetal inflammatory response syndrome may lead to redistribution of blood flow away from the fetal kidney, decreased fetal urinary output and oligohydramnios [10, 36, 54]. This may apply to patients with preterm labor and intact membranes. However, it is noteworthy that the amniocentesis-to-delivery interval was shorter even after adjusting for the presence or absence of AF infection and/or intra-amniotic inflammation. This suggests that another mechanism may be operative. We explored whether the frequency of SGA was a potential explanation but found no difference in the rate of this complication between patients with an AFI of >5 cm and those with an AFI of ≤ 5 cm.

Strength and limitations of this study

The strength of our study is that it included a consecutively collected large cohort of patients with preterm labor and intact membranes delivered at the institution allowing for near complete ascertainment of outcome data. Thus, the results of this study are more applicable in this specific clinical condition. A limitation is that in contrast to studies of preterm PROM, the interval between amniocentesis and delivery of most patients was long, limiting the meaningful relationship between placental pathology, umbilical cord analysis and the findings of amniocentesis.

Clinical Implications

Patients with preterm labor and intact membranes and an AFI of ≤ 5 cm are at increased risk for intra-amniotic inflammation and shorter amniocentesis-to-delivery intervals. Thus, this information can be used for counseling patients about their risk for delivery and the need to assess the AF for inflammation. Previous studies have reported that intra-amniotic inflammation is associated with preterm labor [4-7, 12-13, 15, 18-19, 21-24, 27-29, 31-34, 38, 41-43, 47-49] and is a risk factor for adverse outcome [2, 14, 16, 26, 39, 45, 52-53, 56-57].

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Figure 1. Amniotic fluid matrix metalloproteinase-8 (MMP-8) concentrations according to amniotic fluid volume in patients with preterm labor and intact membranes

Patients with oligohydramnios had a significantly higher median amniotic fluid MMP-8 than those with normal amniotic volume (median 664.2 [range 16.6 – 3424.7] ng/ml vs. median 2.3 [range <0.3 – 6142.6] ng/ml; $p < .01$).

AFI, amniotic fluid index

Figure 2. Survival analysis of amniocentesis-to-delivery interval according to amniotic fluid volume in patients with preterm labor and intact membranes

Amniocentesis-to-delivery interval was significantly shorter in patients with oligohydramnios (solid line) than in those with normal amniotic fluid volume (open circles) (median, 18 hours; range, 0-74hours; vs. median, 311 hours; range, 0-3228 hours; $P < .01$). AFI, amniotic fluid index

Table 1

Characteristics of patients and pregnancy outcomes according to amniotic volume

	AFI greater than 5 cm (n=265)	AFI less than 5 cm (n=7)	P
Age (y, mean±SD)	30.2 ± 4.2	33.9 ± 6.0	NS
Nulliparous (No.)	125 (47%)	4 (57%)	NS
Gestational age at amniocentesis (wk, median and range)	31.3 (16.1-34.9)	30.3 (21.3-33.9)	NS
Positive AF culture results (No.)	21 (8%)	1 (14%)	NS
AF MMP-8 > 23 ng/mL (No.)	80 (30%)	6 (86%)	<.01
Positive AF culture and/or AF MMP-8>23 ng/ml (No.)	87 (33%)	6 (86%)	<.01
Clinical chorioamnionitis (No.)	15 (6%)	1 (14%)	NS
Histologic chorioamnionitis (No.)	78/182 (43%)	2/5 (40%)	NS
Gestational age at delivery (wk, median and range)	34.3 (16.6-41.7)	30.4 (21.4-33.9)	<.05
Birth weight (g, mean±SD)	2138 ± 940	1356 ± 690	<.05
Small for gestational age (No.)	15 (6%)	1 (14%)	NS
Cord blood pH<7.15	20/207 (10%)	0/4 (0%)	NS
Cord blood pH (median and range)	7.270 (6.854-7.454)	7.295 (7.220-7.389)	NS
1-min Apgar score<7	99 (37%)	5 (71%)	NS
5-min Apgar score<7	67 (25%)	3 (43%)	NS

AFI, amniotic fluid index; AF, amniotic fluid; MMP-8, matrix metalloproteinase-8; NS, Not significant

Table 2

Clinical information of patients with oligohydramnios

Patients No	GA at amniocentesis	GA at delivery	Mode of Delivery	AF culture	AF MMP-8 (ng/mL)	Remarks
1	32.7	32.9	VD	(-)	16.6	Spontaneous ROM after USG
2	33.9	33.9	VD	(-)	119.6	Artificial ROM during labor
3	28.3	28.4	CS	(+)	1535.9	Cesarean section due to fetal distress
4	30.3	30.4	CS	(-)	75.6	Cesarean section due to placental abruption
5	33.6	33.6	CS	NA	664.2	Cesarean section due to fetal distress
6	21.3	21.4	VD	(-)	1773	Spontaneous ROM after USG
7	27.4	27.9	VD	(-)	3424.7	Spontaneous ROM after USG

GA, gestational age; VD, vaginal delivery; CS, Cesarean section; NA, not available; AF, amniotic fluid; MMP-8, matrix metalloproteinase-8; ROM, rupture of membranes; USG, ultrasonography