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## Patients with an asymptomatic short cervix ( $\leq 15$ mm) have a high rate of subclinical intraamniotic inflammation: implications for patient counseling

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### Abstract

**Objective**—The objective of the study was to determine the frequency and clinical significance of intraamniotic inflammation in asymptomatic women with a sonographic short cervix (SCX) in the midtrimester.

**Study Design**—This cohort study included 47 asymptomatic women (14–24 weeks) with an SCX ( $\leq 15$  mm) who underwent amniocentesis. Women with multiple gestation, cerclage, or cervical dilatation greater than 2 cm were excluded. Intraamniotic inflammation was defined as an elevated amniotic fluid (AF) matrix metalloproteinase-8 concentration ( $>23$  ng/mL).

**Results**—(1) intraamniotic infection was found in 4.3% of patients; (2) among patients with a negative AF culture, the prevalence of intraamniotic inflammation was 22.2%; and (3) patients with a negative AF culture, but with intraamniotic inflammation, had a higher rate of delivery within 7 days (40% vs 5.7%;  $P = .016$ ) and a shorter median diagnosis-to-delivery interval than those without intraamniotic inflammation (18 vs 42 days;  $P = .01$ ).

**Conclusion**—Twenty-two percent of patients with a midtrimester SCX have intraamniotic inflammation. The risk of preterm delivery within 7 days for these patients is 40%.

### Keywords

cervical length; intraamniotic inflammation; matrix metalloproteinase-8; MMP-8; pregnancy; prematurity; preterm delivery

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A sonographic short cervix (SCX) in the midtrimester of pregnancy is a powerful predictor of a subsequent spontaneous preterm delivery.<sup>1-9</sup> The shorter the sonographic cervical length, the higher is the risk of spontaneous preterm labor/delivery,<sup>1-4,6</sup> and asymptomatic women between 14 and 24 weeks of gestation with a cervical length of 15 mm or less have a nearly 50% rate of spontaneous preterm delivery at 32 weeks or less.<sup>4,6</sup>

The importance of identifying asymptomatic patients with a sonographic SCX in the midtrimester derives from the evidence that these patients, whether or not they have a history of preterm birth, may be candidates for therapeutic interventions such as vaginal progesterone,<sup>10-12</sup> cervical cerclage,<sup>13-16</sup> antibiotics,<sup>17</sup> or indomethacin.<sup>18</sup> However, these therapeutic measures may not be beneficial in all patients.<sup>15,18-22</sup> Thus, the clinical management of an asymptomatic pregnant woman with a sonographic SCX in the midtrimester is still an obstetrical challenge.

A plausible explanation for the lack of a single effective treatment is that a sonographic SCX is a syndrome that may be caused by multiple etiologies.<sup>23,24</sup> Of note, intraamniotic infection has been recently implicated in the pathophysiology of asymptomatic short cervix. Indeed, the subclinical microbial invasion of the amniotic cavity has been detected in 9% of patients with a sonographic cervical length less than 25 mm.<sup>17</sup>

Among patients with preterm labor and intact membranes<sup>25</sup> or with preterm prelabor rupture of membranes (PROM),<sup>26</sup> intraamniotic inflammation, regardless of the microbial status of the amniotic cavity, has been associated with similar adverse pregnancy outcomes as in cases with a proven intraamniotic infection. Recently an association between an SCX ( $\leq 5$  mm) in the midtrimester and elevated concentrations of inflammatory cytokines in amniotic fluid has been proposed.<sup>27</sup>

Matrix metalloproteinase (MMP)-8, also known as neutrophil collagenase, is a sensitive marker of inflammation.<sup>28,29</sup> Amniotic fluid MMP-8 concentration has been demonstrated to be a superior index of intraamniotic inflammation than amniotic fluid white blood cell (WBC) count or interleukin (IL)-6.<sup>30</sup>

The aims of this study were to determine the frequency and clinical significance of intraamniotic inflammation (defined by amniotic fluid MMP-8 concentration) in asymptomatic women in the midtrimester of pregnancy with a sonographic SCX and to examine whether there is a relationship between amniotic fluid and maternal plasma MMP-8 concentrations.

## Materials and Methods

### Study population

This retrospective cohort study consisted of women with a singleton pregnancy admitted to Hutzell Women's Hospital, between January 2002 and June 2008, with the diagnosis of an asymptomatic SCX. Using a computer-based search of our clinical and sonographic databases, consecutive patients with a cervical length of 15 mm or less diagnosed between 14 and 24 weeks of gestation, as determined by a documented transvaginal ultrasound examination (TVUS) and those who underwent an amniocentesis within 1 week of diagnosis were identified.

Patients with 1 or more of the following conditions were excluded: (1) multifetal pregnancy; (2) preterm labor or preterm PROM at the time of diagnosis; (3) a cervical cerclage (placed before or after the diagnosis of an SCX); (4) cervical dilatation greater than 2 cm by digital

examination; (5) placenta previa; and (6) fetuses with chromosomal and/or congenital anomalies.

Patients included in this study were enrolled in a longitudinal protocol whose aim was to identify biochemical markers for the prediction of adverse pregnancy outcomes. As part of this protocol, patients are followed with TVUS every 2-4 weeks beginning as early as 14 weeks of gestation. A fraction of patients included in this study were diagnosed with an SCX during a routine TVUS examination and were sent to labor and delivery for further evaluation. Patients who agreed to participate were enrolled in our protocol and a repeat TVUS examination was performed. Digital assessment of the cervix was performed in all patients. The ultrasound findings were recorded and stored in a dedicated database. After the diagnosis of an SCX was made, the patients were referred to the labor and delivery ward for further evaluation and management. Both the sonographic cervical length and the result of the digital vaginal examination were available to the managing physicians.

In our institution, the majority of patients newly diagnosed with a sonographic cervical length less than 25 mm in the midtrimester undergo an initial evaluation during which patients are assessed for signs and symptoms of preterm labor. If preterm labor is ruled out, tocolysis and prophylactic antibiotics are not administered. In addition, these patients are offered an amniocentesis to determine the microbial status of the amniotic cavity, as previous observations suggested an association between SCX and histologic chorioamnionitis<sup>31</sup> and intraamniotic infection.<sup>17,20</sup> Patients were counseled by clinicians, and those who agreed to undergo an amniocentesis as part of their clinical management were asked to donate amniotic fluid and allow collection of clinical information for research purposes. Further management of these patients was at the discretion of the attending physician.

All participating women provided written informed consent prior to the collection of amniotic fluid and maternal blood samples. The use of clinical and ultrasound data and the utilization of samples for research purposes was approved by the institutional review boards of Wayne State University and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (National Institutes of Health, Department of Health and Human Services). Some of these samples have been used previously to study microbial invasion of the amniotic cavity and other biological markers of disease.

### Definitions and study procedures

Gestational age was determined by the last menstrual period or by ultrasound if the sonographic determination of gestational age was not consistent with the last menstrual period dating by more than 1 week. Gestational age at diagnosis was defined as the earliest gestational age at which a cervical length of 15 mm or less was recorded.

Data regarding pregnancy outcomes were obtained from the clinical and research records. Patients who were lost to follow-up and for whom delivery data were not available were censored from the last available follow-up visit. Spontaneous preterm labor was defined by the presence of regular uterine contractions occurring at a frequency of at least 2 every 10 minutes associated with cervical changes before 37 completed weeks of gestation.

Intraamniotic infection was defined as a positive amniotic fluid culture for microorganisms (aerobic/anaerobic bacteria or genital mycoplasmas). Intraamniotic inflammation was defined as an amniotic fluid MMP-8 concentration greater than 23 ng/mL,<sup>32-34</sup> as determined by enzyme-linked immunosorbent assay. Based on the results of the amniotic fluid culture and the amniotic fluid MMP-8 concentration, patients were classified as having 1 of the following conditions: (1) intraamniotic infection; (2) intraamniotic inflammation

without intraamniotic infection; and (3) no intraamniotic infection or inflammation. Histologic chorioamnionitis was diagnosed based on the presence of inflammatory cells in the chorionic plate and/or chorioamniotic membranes,<sup>35</sup> and acute funisitis was diagnosed by the presence of neutrophils in the wall of the umbilical vessels and/or Wharton's jelly, using the criteria previously described.<sup>36</sup>

### **Sonographic assessment of the cervix**

Transvaginal ultrasound examination was conducted with commercially available 2-dimensional and 3-dimensional ultrasound systems (Acuson Sequoia; Siemens Medical Systems, Mountain View, CA, and Voluson E8; GE Healthcare, Milwaukee, WI) equipped with endovaginal transducers with frequency ranges of 5–7.5 and 5–9 MHz, respectively. All sonographic examinations of the cervical length were performed by registered diagnostic medical sonographers using a technique previously described<sup>1,2</sup> and reviewed by an experienced physician.

### **Sample collection**

Amniotic fluid samples were obtained by transabdominal amniocentesis, transported to the laboratory in a sterile capped syringe, and cultured for aerobic/anaerobic bacteria and genital mycoplasmas. WBC count, glucose concentration, and Gram stain were also performed shortly after the amniotic fluid collection. The results of these tests were used for the clinical management of the patients. Amniotic fluid not required for clinical assessment was centrifuged for 10 minutes at 4°C, and the supernatant was aliquoted and stored at –70°C until analysis.

Maternal blood samples were collected into Vacutainer (Becton Dickinson, Franklin Lakes, NJ) tubes immediately before or after the amniocentesis. The samples were then centrifuged at 1300 × g for 10 minutes at 4°C and the obtained plasma was stored at –70°C until assayed.

Following delivery, the placenta, umbilical cord, and chorioamniotic membranes were collected and the presence or absence of histologic chorioamnionitis and/or funisitis was assessed.

### **Determination of MMP-8 concentration**

Amniotic fluid and maternal plasma concentrations of MMP-8 were determined by sensitive enzyme-linked immunoassays (GE Healthcare/Amersham Pharmacia Biotech Inc, Piscataway, NJ). Immunoassays were carried out according to the manufacturer's recommendations. The calculated inter- and intraassay coefficients of variation for MMP-8 immunoassays in our laboratory were 1.7% and 3.9%, respectively, and the sensitivity was 0.101 ng/mL.

### **Statistical analysis**

Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test for normal distribution of the data. As amniotic fluid and maternal plasma MMP-8 concentrations were not normally distributed, Mann-Whitney *U* test was used for comparisons of continuous variables. Comparisons of proportions among groups were performed using Fisher's exact test for categorical variables.

Correlations between amniotic fluid MMP-8 concentrations and cervical length at diagnosis, gestational age at amniocentesis, diagnosis-to-delivery interval, and maternal plasma MMP-8 concentrations were examined using Spearman's rank correlation test. Multivariate logistic regression analysis was performed to determine the relationship between the

amniotic fluid MMP-8 concentrations (as a categorical variable of  $\leq 23$  ng/mL and  $> 23$  ng/mL), gestational age at diagnosis, and cervical length in the prediction of preterm delivery within 7 days from diagnosis.

A Kaplan-Meier survival analysis was performed to assess the diagnosis-to-delivery interval according to the presence or absence of intraamniotic inflammation. A  $P < .05$  was considered statistically significant. The statistical package used was SPSS version 12.0 (SPSS Inc, Chicago, IL).

## Results

### Demographic and clinical characteristics of the study population

During the study period, 53 asymptomatic patients who met the inclusion criteria were identified. Amniotic fluid samples for retrospective analysis of MMP-8 concentration were not available for 6 patients; thus, 47 women (88.7%) were included in the final analysis.

The overall rate of intraamniotic inflammation was 23.4% (11/47). Intraamniotic infection was identified in 2 of 47 patients (4.3%). Amniotic fluid WBC count of 100 cells/mm<sup>3</sup> or greater was found in 3 of 47 patients (6.4%). Among patients with a negative amniotic fluid culture for microorganisms, the rate of intraamniotic inflammation was 22.2% (10/45), whereas only 4.4% (2/45) had an amniotic fluid WBC count of 100 cells/mm<sup>3</sup> or greater.

Of the 2 patients with intraamniotic infection, 1 had a positive amniotic fluid culture for *Fusobacterium nucleatum*. This patient developed clinical chorioamnionitis shortly after admission and labor was induced. The second patient had a positive amniotic fluid culture for *ureaplasma urealyticum* (without intraamniotic inflammation) and received intravenous azithromycin for 7 days with a subsequent term delivery.

Of the 45 patients without intraamniotic infection, 1 patient was lost to follow-up from 32 weeks of gestation, 8 patients (18.2%) delivered at term, and 36 (81.8%) had a spontaneous preterm delivery before 37 completed weeks of gestation. Spontaneous preterm delivery followed a spontaneous preterm labor in 24 patients (67%) and preterm PROM in 12 patients (33%) (2 patients were induced following preterm PROM because of clinical chorioamnionitis).

Table 1 displays the demographic and clinical characteristics of patients with a negative amniotic fluid culture, with (n = 10) and without (n = 35) intraamniotic inflammation. The gestational age range of patients included in this study was 16 weeks and 3 days to 24 weeks of gestation. Patients with intraamniotic inflammation had a shorter gestational age at diagnosis and a lower cervical length than those without intraamniotic inflammation.

### Pregnancy outcome of women with a negative amniotic fluid culture, with and without intraamniotic inflammation

Among women with a negative amniotic fluid culture for microorganisms, patients with intraamniotic inflammation had a shorter median diagnosis-to-delivery interval than those without this condition (21.5 days; interquartile range [IQR], 5.5–51.5 vs 42 days; IQR, 22.7–108;  $P = .035$ ). None of the patients delivered within 48 hours of amniocentesis.

Women with intraamniotic inflammation had a higher rate of preterm delivery within 1 week than those without intraamniotic inflammation (40% [4/10] vs 5.7% [2/35];  $P = .016$ ). The rate of preterm delivery less than 32 weeks of gestation, although higher among patients with intraamniotic inflammation, did not differ significantly between the 2 groups of

patients (those with intraamniotic inflammation: 80% [8/10] vs those without intraamniotic inflammation: 57% [20/35];  $P = .17$ ) (Table 1).

Among patients without intraamniotic infection, the concentration of MMP-8 in amniotic fluid inversely correlated with cervical length at diagnosis ( $r = -0.41$ ;  $P = .005$ ) and with diagnosis-to-delivery interval ( $r = -0.42$ ;  $P = .004$ ). There was no significant correlation between amniotic fluid MMP-8 concentrations and gestational age at amniocentesis ( $r = 0.21$ ;  $P = .16$ ).

Kaplan-Meier survival curves of patients with a negative amniotic fluid culture, with and without intraamniotic inflammation, are displayed in the Figure. One patient was lost to follow-up and was censored at 32 weeks (the last available follow-up visit). None of the patients underwent labor induction before 37 weeks because of conditions not directly related to the diagnosis of a short cervix such as clinical chorioamnionitis or preterm PROM. All undelivered patients were censored at term (37 weeks of gestation). The survival curves of patients with and without intraamniotic inflammation differed significantly (log rank,  $P = .0018$ ).

A multivariate logistic regression analysis was used to explore the relationship between intraamniotic inflammation (amniotic fluid MMP-8 concentration  $>23$  ng/mL), cervical length (millimeters), and gestational age at diagnosis (weeks) in the prediction of preterm delivery within 7 days. In this model, only intraamniotic inflammation was independently associated with a preterm delivery within 1 week after adjustment for gestational age at diagnosis and cervical length (Table 2). In this model there was no significant interaction between cervical length (millimeters) and MMP-8 concentration greater than 23 ng/mL for the prediction of preterm delivery within 7 days.

### **MMP-8 in maternal plasma samples of patients with a short cervix with and without intraamniotic inflammation**

Maternal blood samples taken within 72 hours from amniocentesis were available for 37 patients (8/11 of those with and 29/36 of those without intraamniotic inflammation). A 72 hour interval was chosen to preserve a meaningful temporal relationship between amniotic fluid and maternal plasma MMP-8 concentrations. The median maternal plasma MMP-8 concentration did not differ significantly between women with and without intraamniotic inflammation (51.9 ng/mL; IQR, 31.5–115.1 vs 42.5 ng/mL; IQR, 29–56.7; respectively;  $P = .41$ ). In addition, there was no significant correlation between amniotic fluid and maternal plasma MMP-8 concentrations ( $r = 0.22$ ;  $P = .2$ ).

### **Intraamniotic inflammation and histologic chorioamnionitis**

Placental histopathologic examination was available for 91% of patients (41/45) with a negative amniotic fluid culture. All patients with intraamniotic inflammation (9/9) had placental lesions consistent with histologic chorioamnionitis, whereas only 59% of patients (19/32) without intraamniotic inflammation had such lesions ( $P = .02$ ).

## **Comment**

### **Principal findings of this study**

The principal findings of the study included the following: (1) almost a fourth of asymptomatic patients with a sonographic short cervix ( $\leq 15$  mm) diagnosed between 14 and 24 weeks of gestation had intraamniotic inflammation, and 4.3% of the patients had proven intraamniotic infection; (2) 40% of patients with intraamniotic inflammation, but a negative amniotic fluid culture, delivered within 1 week from amniocentesis; (3) women with

intraamniotic inflammation had a shorter median diagnosis-to-delivery interval than those without this condition; (4) amniotic fluid MMP-8 concentrations inversely correlated with cervical length and diagnosis-to-delivery interval; and (5) intraamniotic inflammation was not reflected in maternal plasma.

The role of intraamniotic infection and/or inflammation in preterm parturition has been a subject of extensive discussion in the literature. Space limitation precludes presentation of the evidence concerning the causative link between intraamniotic infection and preterm parturition, and the interested readers are kindly referred to review articles addressing this issue.<sup>37,38</sup>

Intraamniotic inflammation, regardless of the presence or absence of intraamniotic infection, has been reported to be associated with adverse pregnancy outcomes in several obstetrical conditions including preterm labor,<sup>25,39,40</sup> preterm PROM,<sup>26,30</sup> and cervical insufficiency.<sup>34</sup> Furthermore, elevated markers of intraamniotic inflammation at the time of genetic amniocentesis were associated with subsequent pregnancy loss or preterm delivery.<sup>32,41,42</sup>

The value of MMP-8 concentration in amniotic fluid as a predictor of intraamniotic infection and/or inflammation and adverse pregnancy outcome is well established,<sup>30,32,43,44</sup> and its superior performance over other inflammatory markers (ie, WBC count, IL-6, angiogenin) in the detection of intraamniotic infection/inflammation has been previously reported.<sup>30,32,40</sup>

The association between intraamniotic infection and an asymptomatic SCX has been first proposed by our group.<sup>17</sup> In that study, subclinical microbial invasion of the amniotic cavity (MIAC) was evident in 9% of patients (5/57) with a sonographic SCX (defined as <25 mm) diagnosed at 14-24 weeks. Recently Kiefer et al<sup>27</sup> proposed an association between a cervical length of 5 mm or less in the midtrimester and increased amniotic fluid concentrations of inflammatory cytokines such as monocyte chemotactic protein (MCP)-1 and IL-6. Keeler and colleagues<sup>45</sup> in a subsequent study of 44 patients in the midtrimester with a cervical length of 25 mm or less, in which those with intraamniotic infection and/or signs of preterm labor were not excluded, reported that amniotic fluid MCP-1 was predictive of spontaneous preterm delivery. Of note, 16% of these patients delivered spontaneously within 48 hours.<sup>45</sup>

In contrast, the results of the present study provide information concerning pregnancy outcome of patients with intraamniotic inflammation in the presence of a negative amniotic fluid culture (including for *Ureaplasma urealyticum* and *Mycoplasma hominis*, which are prevalent microorganisms causing intraamniotic infection<sup>17,26,32,46,47</sup>). Furthermore, our study specifically concentrated on asymptomatic patients without intraamniotic infection, advanced cervical dilatation, or premature contractions/labor (conditions that have been previously linked to intraamniotic inflammation<sup>25,34,39,40</sup>), and the fact that none of the patients in our study delivered within 48 hours supports the notion that these patients were completely asymptomatic.

This study demonstrates that intraamniotic inflammation, even in the absence of MIAC, is a risk factor for preterm delivery within 7 days of the diagnosis of a short cervix in asymptomatic patients in the second trimester of pregnancy. Indeed, intraamniotic inflammation has been identified in 22% of patients with a negative amniotic fluid culture, which is similar to the rate described for preterm labor (23%; 44/185),<sup>25</sup> whereas it was lower than in those with preterm PROM (30%; 51/169)<sup>26</sup> or cervical insufficiency (79%; 38/48).<sup>34</sup>

Kiefer et al<sup>27</sup> reported that the concentrations of the inflammatory cytokines MCP-1, IL-6, and IL-8 appeared to become elevated at a cervical length of 5 mm or less. This finding is in agreement with the results of our study, which showed that amniotic fluid MMP-8 concentration significantly correlated with cervical length at diagnosis and that 73% (8/11) of patients with intraamniotic inflammation had a cervical length of 5 mm or less.

This information may be of clinical importance when counseling these patients regarding therapeutic interventions. Indeed, despite the promising results of some randomized clinical trials,<sup>10,48</sup> other studies have reported no beneficial effect of therapeutic measures used in patients with an asymptomatic SCX.<sup>15,18-22</sup> Fonseca et al<sup>10</sup> reported an overall 44% reduction in the rate of preterm birth in women with a cervical length of 15 mm or less. In women with an extremely SCX (<5 mm), however, progesterone administration was less effective (10%) (K. H. Nicolaides, personal communication<sup>49</sup>).

One plausible explanation for the high failure rate in patients with a very SCX is that this subset of women may have already developed asymptomatic intrauterine infection and/or inflammation and may already have entered into the irreversible phase of parturition, in which available interventions to prolong pregnancy such as cervical cerclage or progesterone administration are ineffective. This view is supported by our observation that 40% of the patients with intraamniotic inflammation without proven MIAC delivered within 7 days. This association remained significant after adjusting for gestational age and cervical length at diagnosis, both of which had previously been reported to be inversely correlated with the risk of preterm delivery.<sup>2,50,51</sup> Importantly, MMP-8 concentration in maternal plasma was not informative of the status of the amniotic cavity, and there was no significant correlation between the concentrations of MMP-8 in the maternal and fetal compartments, further demonstrating the value of amniocentesis because of the independent nature of these 2 compartments.

The etiologic factors responsible for the intraamniotic inflammation in the presence of a negative amniotic fluid culture in patients with an asymptomatic SCX remain to be elucidated. However, several possible explanations can account for our findings. First, it is possible that some microbial invasion of the amniotic cavity cannot be detected by standard microbiological cultivation techniques. Of note, only about 1% of the whole microbial world can be detected by cultivation techniques.<sup>52-54</sup> Indeed, using molecular microbiology techniques, microbial footprints can be detected in women with a negative amniotic fluid culture.<sup>55-61</sup> Second, some women with a negative amniotic fluid culture may have intrauterine infection of the extraamniotic space with an intraamniotic inflammatory response.<sup>37,62</sup> Third, recently the presence of amniotic fluid sludge,<sup>63-66</sup> a cluster of particulate matter in the amniotic fluid in close proximity to the cervix, has been shown to represent, at least in some cases, microbial biofilms.<sup>67</sup> Detection of microbial invasion of the amniotic cavity in the presence of biofilms is challenging, and current cultivation techniques are inadequate to identify such infections.<sup>67</sup> Finally, the inflammatory response detected in amniotic fluid may be a consequence of a sterile inflammatory response activated by nonmicrobial endogenous danger signals such as cellular alarm signals from distressed and injured cells or tissues.<sup>68-72</sup> It remains to be elucidated which of the aforementioned suggested mechanisms is indeed associated with intraamniotic inflammation and whether therapeutic interventions can modulate the inflammatory response detected in asymptomatic patients with an SCX.

### Strengths and limitations

One of the strengths of this study is that it is the first to provide evidence that intraamniotic inflammation in asymptomatic patients with an SCX, in the absence of intraamniotic



infection, is associated with adverse pregnancy outcome. These findings can be beneficial to clinicians in the counseling and clinical management of these challenging patients.

The limitations of this study rest on its relatively small sample size. However, the prevalence of a sonographic cervical length of 15 mm or less at 14-24 weeks in our population is around 0.6%.<sup>6</sup> This relatively low prevalence and the fact that not all patients had amniocentesis coupled with the strict inclusion criteria used in this study make it difficult to obtain a much larger sample size.

Another potential limitation is that not all women agreed to undergo an amniocentesis. The reasons that some women agreed to have an amniocentesis and others do not are unknown. Several attending clinicians were involved in counseling patients regarding amniocentesis, and although there is no evidence that a bias was introduced by the individual who counseled the patient, neither can we exclude such a bias. In addition, because of the retrospective nature of this study, amniotic fluid and maternal plasma samples for MMP-8 assay were not available for all patients.

## Conclusions

One of every 4 patients with a sonographic SCX ( $\leq 15$  mm) before 24 weeks has subclinical intraamniotic infection and/or inflammation. The risk of spontaneous preterm delivery within 7 days among patients without intraamniotic infection but with intraamniotic inflammation is 40%. These findings have implications for the counseling and management of patients with an asymptomatic SCX.

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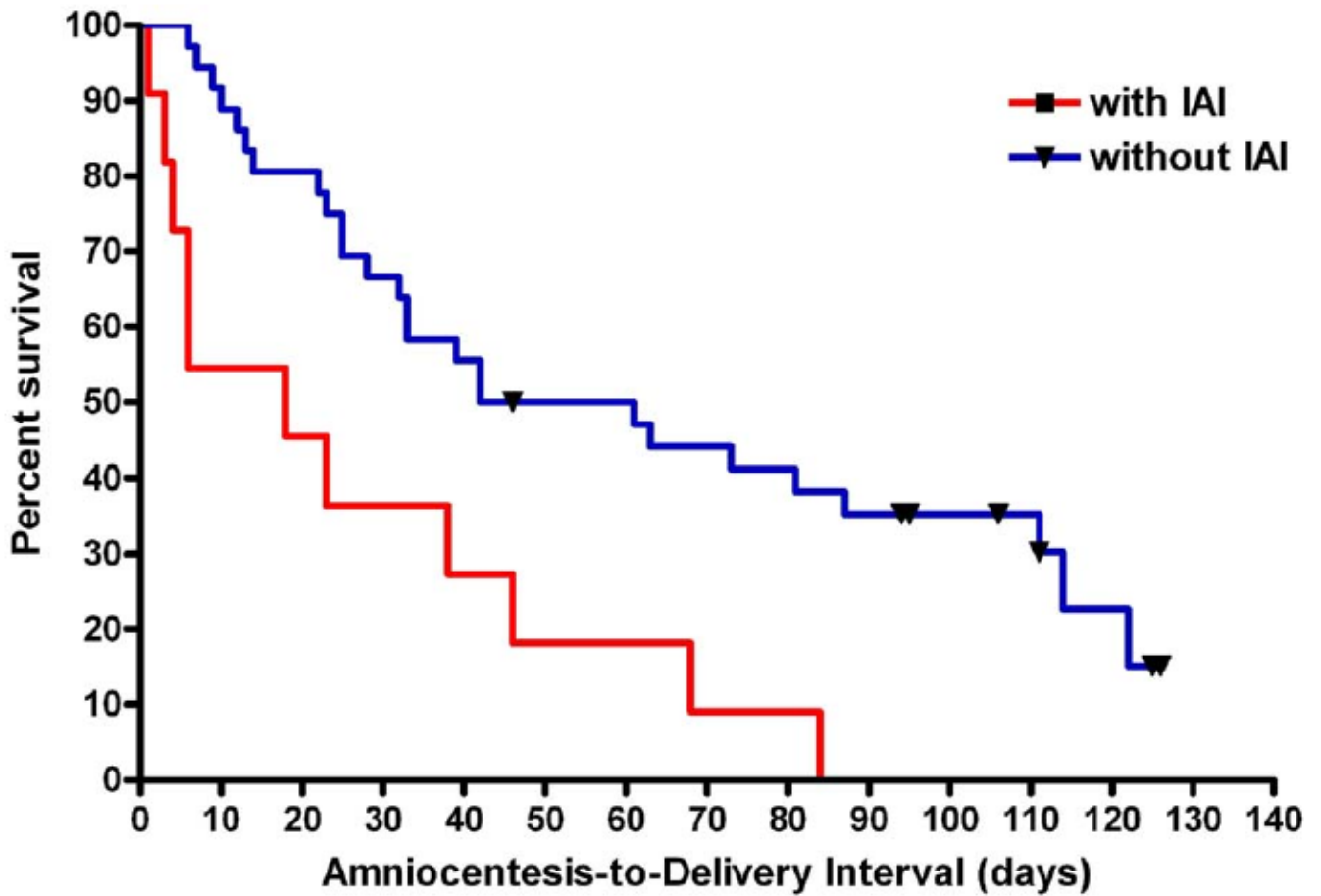
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**FIGURE. Kaplan-Meier survival curves**

Kaplan-Meier survival curves of patients with a negative amniotic fluid culture, with and without intraamniotic inflammation (IAI). One patient was censored at 32 weeks because of loss to follow-up, and all other patients were censored at 37 completed weeks of gestation (*black symbols* at censored observations). The 2 curves differed significantly (log rank,  $P = .0018$ )

**TABLE 1**  
**Characteristics of patients with a negative amniotic fluid culture**

Characteristic	Without intraamniotic inflammation (n = 35)	With intraamniotic inflammation (n = 10)	P value
Age, y	23 (20–29)	26.5 (21.6–37.6)	.17
African-American ethnic origin	94.3 (33)	80 (8)	.21
Smoker	18.2 (6/33)	33.3 (3/9)	.37
Prepregnancy BMI, kg/m <sup>2</sup>	28.3 (24.1–29.4)	28.3 (22.4–32.3)	.73
Nulliparity	57.1 (20)	50 (5)	.7
History of spontaneous PTD <35 wks	28.6 (10)	50 (5)	.26
Prophylactic 17 $\alpha$ -hydroxyprogesterone caproate	9.4 (3)	10 (1)	1.0
Genital infection during pregnancy	25.7 (9)	20 (2)	1.0
Bacterial vaginosis	11.4 (4)	20 (2)	
Chlamidia trachomatis	8.6 (3)	0 (0)	
Gonorrhea	0 (0)	0 (0)	
Trichomonas	5.7 (2)	0 (0)	
GA at diagnosis, wks	21.1 (19.1–23.1)	23.2 (21.9–23.5)	.044
Cervical length at diagnosis, mm	11 (4–13)	1.5 (0–6.5)	.005
GA at amniocentesis, wks	21.1 (19.1–23.1)	23.2 (22.1–23.5)	.045
Amniotic fluid WBC count $\geq 50$ cells/mm <sup>3</sup>	5.7 (2)	20 (2)	.2
Amniotic fluid WBC count $\geq 100$ cells/mm <sup>3</sup>	2.9 (1)	10 (1)	.4
GA at delivery, wks	28.1 (23.3–36.9)	25.8 (23–30.7)	.12
Birthweight, g	1098 (500–2680)	763 (578–1482)	.18
Diagnosis-to-delivery interval, d	42 (23–107)	21.5 (5.5–51.5)	.026
Delivery within 7 d	5.7 (2)	40 (4)	.016
Spontaneous preterm delivery <32 wks	57.1 (20)	80 (8)	.17
Spontaneous preterm delivery <37 wks	72.2 (26/34)	100 (10)	.17

Numbers are presented as median (interquartile range) or percentage (number).

*BMI*, body mass index; *GA*, gestational age; *PTD*, preterm delivery.

**TABLE 2**  
**Logistic regression for preterm delivery within 7 days of amniocentesis**

Explanatory variable	Odds ratio	95% CI	P value
Gestational age at diagnosis of short cervix, wks	0.46	0.16–1.37	.16
Cervical length, mm	0.29	0.02–3.8	.34
Amniotic fluid MMP-8 concentration >23 ng/mL	55.4	1.1–2807	.045

CI, confidence interval.