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Patients with acute cervical insufficiency without intra-amniotic infection/inflammation treated with cerclage have a good prognosis

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Abstract

Background: The frequency of intra-amniotic infection/inflammation (IAI/I) in patients with midtrimester cervical insufficiency is up to 50%. Our purpose was to determine the perinatal outcomes of cervical cerclage in patients with acute cervical insufficiency with bulging membranes, and to compare the admission-to-delivery interval and pregnancy outcomes according to the results of amniotic fluid (AF) analysis and cerclage placement.
Methods: This was a retrospective cohort study including singleton pregnancies with cervical insufficiency between 15 and 26.9 weeks in two tertiary health centers. IAI/I was defined when at least one of the following criteria was present in AF: (a) a white blood cell (WBC) count >50 cells/mm^3; (b) glucose concentration <14 mg/dL; and/or (c) a Gram stain positive for bacteria. Three different groups were compared: (1) absence of IAI/I with placement of a cerclage; (2) amniocentesis not performed with placement of a cerclage; and (3) IAI/I with or without a cerclage.
Results: Seventy patients underwent an amniocentesis to rule out IAI/I. The prevalence of IAI/I was 19%. Forty-seven patients underwent a cerclage. Patients with a cerclage had a longer median admission-to-delivery interval (33 vs. 2 days; $P < 0.001$) and delivered at a higher median gestational age (27.4 vs. 22.6 weeks; $P = 0.001$) than those without a cerclage. The neonatal survival rate in the cerclage group was 62% vs. 23% in those without a cerclage ($P = 0.01$). Patients without IAI/I who underwent a cerclage had a longer median admission-to-delivery interval (43 vs. 1 day; $P < 0.001$), delivered at a higher median gestational age (28 vs. 22.1 weeks; $P = 0.001$) and had a higher neonatal survival rate (67% vs. 8%; $P < 0.001$) than those with IAI/I.
Conclusion: The pregnancy outcomes of patients with midtrimester cervical insufficiency and bulging membranes are poor as they have a high prevalence of IAI/I. Therefore, a pre-operative amniocentesis is key to identify the best candidates for the subsequent placement of a cerclage.

Keywords: amniotic fluid analysis; bulging membranes; cervical cerclage; cervical incompetence; cervical insufficiency; cervical stitch; intra-amniotic infection;

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intra-amniotic inflammation; MIAC; microbial invasion of the amniotic cavity.

Introduction

Cervical insufficiency is defined as the inability of the uterine cervix to retain the fetus in the absence of uterine contractions in the second trimester [1–4]. This condition occurs in approximately 0.15%–1% of live births [5–7] during the second trimester of pregnancy, and it is associated with spontaneous abortion, extreme prematurity and adverse obstetrical and neonatal outcomes [7–9]. Cervical cerclage has been successfully used in the management of patients with a history of second trimester losses and progressive shortening of the cervix in the second trimester [10–32], although there is some evidence against its efficacy [33–39]. The most severe form of cervical insufficiency is the passive and painless dilatation of the uterine cervix leading to bulging membranes [40–42], and a solid body of evidence supports the benefit of placing a cerclage in those patients [43–53].

The presence of intra-amniotic infection/inflammation (IAI/I) is associated with adverse pregnancy outcomes in women with spontaneous preterm labor with intact membranes [54–60], preterm prelabor rupture of membranes (pPROM) [61–65] and cervical insufficiency. Indeed, between 13% and 51% of patients with cervical insufficiency and bulging membranes have a positive amniotic fluid (AF) culture and the presence of IAI/I has been consistently associated with a poor prognosis [66–71]. It has been shown that 76% of patients with cervical insufficiency and microbial invasion of the amniotic cavity (MIAC) delivered within the first 48 h of admission [67]. Moreover, Mays et al. [68] reported that patients without intra-amniotic infection managed with cervical cerclage delivered at a significantly higher gestational age and had better neonatal survival rates than those managed without amniocentesis, or than patients with intra-amniotic infection but managed expectantly. Collectively, these results indicate that IAI/I strongly affects the pregnancy outcomes of patients with cervical insufficiency.

The objectives of this study were to determine the perinatal outcomes of cervical cerclage in patients with acute cervical insufficiency with bulging membranes in the second trimester, and to compare the admission-to-delivery interval and pregnancy outcomes according to the results of the AF analysis and cervical cerclage placement.

Materials and methods

Study design and population

This is a retrospective cohort study including all singleton pregnancies between 15 and 26.9 weeks of gestation with the diagnosis of cervical insufficiency and bulging membranes who were admitted at the Hospital Sótero del Río and Clínica Dávila in Santiago, Chile, between January 2009 and May 2017. Exclusion criteria were: (1) patients with the diagnosis of cervical insufficiency due to an asymptomatic short cervix (<25 mm); (2) cases with cervical insufficiency who presented with cervical dilatation at digital examination, but without bulging membranes at speculum examination; (3) patients with the diagnosis of clinical chorioamnionitis at admission; (4) cases for whom there were incomplete or absent records of the results of AF analysis (if an amniocentesis was performed) or pregnancy outcomes; (5) twin gestations; and (6) fetal congenital anomalies.

We retrospectively reviewed all the medical records with the diagnosis of "cervical insufficiency" or "cervical incompetence" at admission and/or discharge, all surgical procedures that included the terms "cervical cerclage" or "cervical stitch" and all the laboratory records of non-genetic amniocenteses performed during the study period. Demographic and clinical characteristics of patients were recorded, as well as data from previous pregnancies, the results of maternal blood laboratory tests, as well as those of AF analysis. Information regarding the inpatient management, pregnancy and neonatal outcomes was also collected. All data obtained from medical records were recorded on a pre-specified database. The use of demographic, clinical, laboratory and sonographic data collected from chart review was approved by the Institutional Review Boards of Hospital Sótero del Río and Clínica Dávila.

The standard management of patients with cervical insufficiency with bulging membranes in the second trimester consists of a preoperatory amniocentesis to exclude IAI/I before the placement of a cervical cerclage. Yet, the final decision of performing an amniocentesis and placing a cerclage was at the discretion of the physician. Women with the diagnosis of IAI/I are usually not considered candidates for a cervical cerclage, and they have expectant management under broad spectrum antibiotic coverage including ceftriaxone and metronidazole, or ceftriaxone and clindamycin, with or without the addition of a macrolide. In patients with IAI/I, induction of labor is not routinely performed, except in cases in which maternal health is considered at risk.

Based on that, patients were classified into the following groups: (1) group 1: absence of IAI/I and managed with cervical cerclage; (2) group 2: amniocentesis not performed and managed with cervical cerclage; and (3) group 3: presence of IAI/I, with or without cervical cerclage.

Definitions

Spontaneous preterm delivery was defined by the presence of regular uterine contractions occurring at a frequency of at least two every 10 min associated with cervical changes before 37 completed weeks, leading to preterm delivery. pPROM was diagnosed by sterile speculum examination confirming pooling of AF in the vagina in association with ferning tests when necessary, before 37 weeks of gestation and in the absence of labor. Clinical chorioamnionitis was diagnosed

according to the criteria proposed by Gibbs et al. [72] including a maternal temperature of ≥37.8°C and two or more of the following criteria: uterine tenderness, malodorous vaginal discharge, maternal leukocytosis (≥15,000 cells/mm^3), maternal tachycardia (>100 beats/min) and fetal tachycardia (>160 beats/min). IAI/I was defined when at least one of the following three criteria was present in AF [73–75]: (a) a white blood cell (WBC) count >50 cells/mm^3; (b) glucose concentration <14 mg/dL; and/or (c) a Gram stain positive for bacteria.

Sample collection

AF was obtained by transabdominal amniocentesis under ultrasonographic guidance. Samples of AF were transported to the laboratory in a sterile capped syringe. AF WBC count, glucose concentration and Gram stain were also performed shortly after collection in all patients as previously described [73, 74]. The results of these tests were used for clinical management. AF cultures for aerobic, anaerobic and genital mycoplasmas were performed at the discretion of the physician.

Statistical analyses

Normality of distribution in numerical variables was tested using the Shapiro-Wilk test. In variables fitting a normal distribution, comparisons between or among groups were made by *t*-test or one-way analysis of variance (ANOVA), as appropriate. In numerical variables not fitting a normal distribution, comparisons were made using the Mann-Whitney *U*-test or Kruskal-Wallis test. Comparisons between or among proportions were performed with chi-square (χ^2) or Fisher's exact tests, as appropriate. The statistical package used was STATA v.14.2 (StataCorp, 2015, Stata Statistical Software: Release 14, StataCorp LP, College Station, TX, USA). A two-tailed, P-value <0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of the study population

Figure 1 shows the disposition of patients who are part of the study. Initially, 105 cases of cervical insufficiency were identified. We excluded: (a) 15 cases of cervical insufficiency in which there was cervical dilatation, but without bulging membranes at speculum evaluation; (b) seven cases of twin pregnancies; (c) two cases presenting <15 weeks; (d) two cases presenting >26$^{6/7}$ weeks; (e) one patient was lost to follow-up; and (f) one case for whom the results of AF analyses were not available.

A total of 77 patients were included in the study. The demographic and clinical data, according to the results of AF analyses, are reported in Table 1. The mean gestational

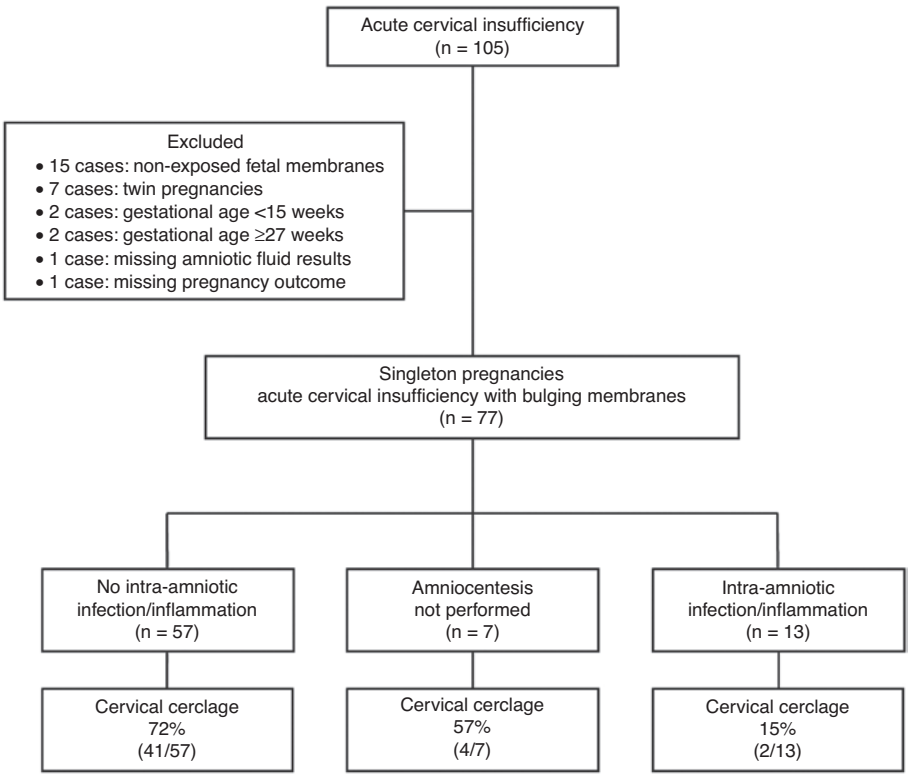

Figure 1: Disposition of patients who are part of the study.

Table 1: Demographic and clinical characteristics of study population at admission, according to the results of amniotic fluid analyses.

	No IAI/I (n = 57)	Amniocentesis not performed (n = 7)	IAI/I (n = 13)	P-value
Maternal age, years	28.4 (±7.3)	25.0 (±7.7)	26.8 (±5.8)	0.429
Gestational age, weeks	21.8 (±2.7)	21.9 (±1.0)	21.8 (±2.4)	0.999
Body mass index, kg/m^2	27.8 (±5.6)	25.1 (±5.3)	30.0 (±5.4)	0.176
Nulliparity	58 (33/57)	71 (5/7)	69 (9/13)	0.675
Prior second trimester loss	18 (10/57)	14 (1/7)	0 (0/13)	0.271
Prior preterm birth	19 (11/57)	0 (0/7)	15 (2/13)	0.602
Prior cervical cerclage	4 (2/57)	0 (0/7)	0 (0/13)	1.000
Uterine malformation	2 (1/57)	14 (1/7)	0 (0/13)	0.201
Active smoking	11 (6/57)	0 (0/7)	0 (0/13)	0.770
Progesterone use before admission	14 (8/57)	0 (0/7)	15 (2/13)	0.731
Cervical dilatation, cm	2.9 ± 1.9	3.7 ± 3.1	4.3 ± 2.1[a]	0.059
Maternal heart rate, bpm	93 ± 12	92 ± 10	101 ± 10[b]	0.081
Body temperature, °C	36.5 ± 0.3	36.3 ± 0.7	36.7 ± 0.5	0.018
White blood cell count, ×10^3/mm^3	11.6 ± 2.5	15.4 ± 6.8	15.1 ± 3.5[c]	0.005
C-reactive protein, mg/L	4.4 ± 5.5	24.5 ± 38.0	19.7 ± 23.8[d]	0.085

Values are expressed as percentage (proportion) or mean (±standard deviation). Bivariate analysis: [a]Comparison between groups "No IAI/I" and "IAI/I": P = 0.015. [b]Comparison between groups "No IAI/I" and "IAI/I": P = 0.033. [c]Comparison between groups "No IAI/I" and "IAI/I": P = 0.002. [d]Comparison between groups "No IAI/I" and "IAI/I": P = 0.025.

age at admission was 21.8 ± 2.5 weeks. Forty-seven (61%) patients were nulliparous, 17% (13/77) had a history of previous spontaneous preterm birth and 14% of patients (11/77) had a history of second trimester pregnancy loss. Two cases (3%) had a history of cervical cerclage due to cervical insufficiency in previous pregnancies, and 13% (10/77) were under vaginal progesterone treatment because of a short cervix.

At admission, 91% (70/77) of patients underwent an amniocentesis to exclude IAI/I. According to the results of the AF analyses, 19% (13/70) of them had IAI/I. Patients with IAI/I had a significantly greater cervical dilatation (mean: 4.3 ± 2.2 vs. 2.9 ± 2.0 cm, P = 0.015), higher maternal WBC count (mean: 15.1 ± 3.5 cells × 10^3/mm^3 vs. 11.6 ± 2.5 cells × 10^3/mm^3, P = 0.002) and higher maternal serum concentrations of C-reactive protein (mean: 19.7 ± 23.8 vs. 4.4 ± 5.5 mg/L, P = 0.025) than patients without IAI/I. No adverse events were observed due to the performance of the amniocenteses.

During the initial evaluation, 34% (26/77) of patients were not considered candidates for a cervical cerclage and underwent expectant management. The main contraindications for cervical cerclage were: (a) presence of IAI/I (11 cases), (b) onset of spontaneous preterm labor within 48 h after admission (nine cases), (c) pPROM within 48 h of admission (two cases), (d) gestational age higher than 25$^{6/7}$ weeks (two cases), (e) current pregnancy with an intrauterine device (one case) and (f) suspected clinical chorioamnionitis occurring within 48 h of admission (one case).

On the other hand, 66% (51/77) of patients were considered candidates for a cervical cerclage and underwent this procedure. In 8% (4/51) of cases, rupture of the membranes occurred during the cerclage. In these cases, the procedure was stopped, and the patients were managed with antibiotic treatment. The remaining 47 patients received a cervical cerclage.

Patients managed with a cervical cerclage had a significantly longer admission-to-delivery interval [median admission-to-delivery interval: 33 days, interquartile range (IQR): 12–89 vs. 2 days, IQR: 1–20, P < 0.001] and delivered at a significantly higher gestational age (median gestational age at delivery: 27.4 weeks, IQR: 23.4–35.9 vs. 22.6 weeks, IQR: 21.4–25.6, P = 0.001) than those who did not have a cerclage. The neonatal survival rate in the cerclage group was 62% (29/47), compared to 23% (7/30) in those without a cerclage (P = 0.01).

Perinatal outcomes according to amniotic fluid analysis and cervical cerclage

Table 2 displays the perinatal outcomes according to the status of the AF and cerclage placement. Patients without

Table 2: Pregnancy outcomes according to amniotic fluid analysis and cerclage.

	Group 1 Cerclage + no IAI/I (n = 41)	P-value[a]	Group 2 Cerclage + amniocentesis not performed (n = 4)	P-value[b]	Group 3 IAI/I (n = 13)	P-value[c]
Admission-to-delivery interval, days	43 (15.0–89.0)	0.675	21.5 (16.0–64.5)	0.010	1 (1.0–10.0)	<0.001
Gestational age at delivery, weeks	28 (23.7–36.3)	0.523	25.4 (24.1–30.4)	0.047	22.1 (20.7–23.4)	0.001
Birth weight, g	1,212 (660–2,890)	0.531	897 (690–1,792)	0.032	550 (435–625)	0.002
Delivery <48 h from admission	2 (1/41)	0.911	0 (0/4)	0.029	69 (9/13)	<0.001
Delivery <7 days from admission	12 (5/41)	0.613	0 (0/4)	0.029	69 (9/13)	<0.001
Delivery <24 weeks	27 (11/41)	0.714	25 (1/4)	0.053	85 (11/13)	0.001
Delivery <28 weeks	49 (20/41)	0.321	75 (3/4)	0.426	92 (12/13)	0.005
Delivery <32 weeks	61 (25/41)	0.511	75 (3/4)	0.235	100 (13/13)	0.005
Neonatal survival[d]	67 (26/39)	0.607	75 (3/4)	0.022	8 (1/13)	<0.001

Values are expressed as percentage (proportion) or median (interquartile range). [a]P-values for comparison between groups 1 and 2. [b]P-values for comparison between groups 2 and 3. [c]P-values for comparison between groups 1 and 3. [d]Two newborns in group 1 were delivered in participating centers and were posteriorly transferred to other centers for neonatal management. No information regarding neonatal survival was available for both cases.

IAI/I who underwent a cervical cerclage had good pregnancy outcomes. The median admission-to-delivery interval was 43 days (IQR: 15–89 days), and the median gestational age at delivery was 28 weeks (IQR: 23.7–36.3 weeks). In this group, the neonatal survival rate was 67% (26/39). There were no significant differences regarding pregnancy outcomes between groups 1 and 2.

In contrast, patients with IAI/I (group 3) had a poor pregnancy outcome. Their median admission-to-delivery interval was 1 day (IQR: 1–10 days), and the median gestational age at delivery was 22.1 weeks (IQR: 20.7–23.4 weeks). This was significantly shorter compared to groups 1 and 2. Moreover, the proportion of patients delivering within the first 48 h and 7 days after admission was significantly higher in group 3 compared with groups 1 and 2. Indeed, 69% of patients presenting with cervical insufficiency with bulging membranes and IAI/I delivered within the first 48 h of admission, and the neonatal survival rate was only 8% (1/13).

There were two patients in group 3 for whom a cervical cerclage was inserted. In both cases, the amniocentesis was performed at the discretion of their physicians at the time of cerclage placement. Unfortunately, the AF analyses were consistent with IAI/I. In both patients, the cervical cerclage was not removed and underwent expectant management with broad spectrum antibiotics. The first case delivered at 23.3 weeks of gestation (11 days after admission), and the second case delivered at 23.4 weeks (1 day after admission). Both neonates died shortly after delivery. The remaining 11 cases of this group were managed expectantly with broad spectrum antibiotics and without a cervical cerclage. Their median admission-to-delivery interval was 1 day (IQR: 1–10 days), and the median gestational age at delivery was 22 weeks (IQR: 20.4–23.9 weeks). Only one neonate survived; this case was admitted at 25.6 weeks of gestation and delivered at 28.6 weeks (23 days after admission).

Discussion

Principal findings of the study

(1) Sixty percent of patients with cervical insufficiency and bulging membranes in the second trimester were nulliparous; (2) patients with a cerclage had a significantly longer admission-to-delivery interval, as well as significantly higher gestational age at delivery and neonatal survival rate than those who did not have a cerclage; (3) patients with cervical insufficiency and bulging membranes without IAI/I, who underwent a cervical cerclage, had a median admission-to-delivery interval of 43 days, a median gestational age at delivery of 28 weeks and a neonatal survival rate of 67%; (4) in contrast, patients with cervical insufficiency and bulging membranes with IAI/I had a median admission-to-delivery interval of 1 day, a median gestational age at delivery of 22 weeks and a neonatal survival rate of 8%; (5) no maternal and fetal adverse events were reported during the performance of the transabdominal amniocenteses; and (6) 8% of patients ruptured the membranes during cerclage.

The role of emergency cerclage in cervical insufficiency

Previous studies have evaluated the effect of cervical cerclage on pregnancy outcomes in women with cervical insufficiency and bulging membranes [43–53, 76–80], reporting the benefits of this intervention. Evidence from a small randomized clinical trial [46] demonstrated that, in women with cervical insufficiency and bulging membranes, placement of a cervical cerclage was associated with a significant longer admission-to-delivery interval, higher gestational age at delivery and lower incidence of preterm birth <34 weeks compared to patients assigned to expectant management. In addition, Ehsanipoor et al. [53] reported a systematic review and meta-analysis including 10 studies [43–52] assessing the effects of cerclage in cases of cervical insufficiency and bulging membranes in the second trimester, showing that an emergency cervical cerclage significantly reduced the risk of preterm delivery <34 weeks, and significantly increased the interval from admission to delivery, gestational age at delivery and overall neonatal survival compared to expectant management. In agreement with those reports, we observed herein that placement of a cervical cerclage was associated with a 31-day increase in the median admission-to-delivery interval compared with expectant management, and with a significant increase in the gestational age at delivery and neonatal survival rates.

Similarly, cervical cerclage has demonstrated benefits in prolongation of gestation when used in populations at high risk of preterm birth [81–83]. A systematic review and meta-analysis of randomized trials reported by Berghella et al. [84], including five trials [85–89], evaluated the effects of cervical cerclage versus no cerclage in patients with a history of preterm birth and a sonographic short cervix (<25 mm) <24 weeks of gestation. Placement of a cervical cerclage was associated with a significant reduction in the risk of preterm birth and perinatal morbidity and mortality.

Cervical insufficiency and intra-amniotic infection/inflammation

In this study, 91% of patients with cervical insufficiency and bulging membranes in the second trimester underwent an amniocentesis to rule out IAI/I before placement of a cervical cerclage, and 34% of patients were not considered candidates for a cervical cerclage mainly due to the presence of signs of IAI/I or onset of labor shortly after admission. The role of IAI/I and its effects over the outcome of pregnancies in women with cervical insufficiency with bulging membranes is well established in the literature [67–71, 90, 91]. The incidence of subclinical intra-amniotic infection demonstrated by AF cultures has been reported as high as 51% [67, 69]. In the present study, the prevalence of IAI/I (based on AF Gram stain, WBC count and glucose concentration) was 19%. In a similar population, Mays et al. [68], using AF lactate dehydrogenase and glucose concentrations, reported 38% (7/18) of amniocentesis suggesting IAI/A. Also, Diago-Almela et al. [92], using a combination of AF concentrations of interleukin-6, glucose, WBC count and leucocyte esterase test, reported an incidence of IAI/I of 64% (20/31). The mean gestational age at delivery in patients without IAI/I was 35.1 weeks, and the reported neonatal survival was 100%. The prevalence of IAI/I in our study was lower compared to what has been previously reported, probably due to the lower diagnostic performance of the AF markers used for detecting cases of IAI/I. In our study, patients with IAI/I had a median admission-to-delivery interval of only 1 day (IQR: 1–10). Moreover, 69% of these cases had labor and delivered within 48 h from admission. These results are consistent with previous studies. Other reports [67, 70] suggest that in patients with cervical insufficiency, bulging membranes and an amniocentesis suggesting IAI/I, the rates of delivery within 48 h from admission were between 50% and 76%. In addition, Mays et al. [68] reported that the mean admission-to-delivery interval in patients with IAI/I was 3.8 ± 4.6 days, which is similar to what was found in our study.

On the other hand, performing a cervical cerclage in patients without IAI/I increases the possibilities of achieving a favorable pregnancy outcome. Mays et al. [68] reported a mean gestational age at delivery of 35.2 ± 4.2 weeks in this subgroup of patients, with a mean admission-to-delivery interval of 93.4 ± 33.1 days. Similarly, Diago-Almela et al. [92] reported a mean gestational age at delivery of 35.4 weeks, with a mean admission-to-delivery interval of 89 days. These latency periods are higher than those observed in our study. This may be explained by the differences in diagnostic criteria used for establishing the diagnosis of IAI/I, and differences in the magnitude of cervical dilatation at admission (2.5 ± 0.8 cm in Mays et al. and 2.9 ± 1.9 cm in our study). In previous reports, advanced cervical dilatation with protrusion of membranes through external os has been systematically associated with adverse pregnancy outcomes [91, 93–104]. In this study, advanced cervical dilatation with bulging membranes was not considered an exclusion criterion for cervical cerclage placement.

Altogether, these findings suggest that a significant proportion of patients with cervical insufficiency are affected by IAI/I, and that delivery will occur soon after admission

as the optimal management of patients with IAI/I has not been determined. Performing a cervical cerclage in patients with IAI/I may be harmful for the mother and fetus, and also ineffective in increasing the admission-to-delivery interval.

Strength and limitations

To our knowledge, this is the largest study reporting patients who underwent an amniocentesis before cerclage placement. The fact that patients with cervical insufficiency and bulging membranes without IAI/I, who underwent a cervical cerclage, had a neonatal survival rate of 67% is a major finding. This study has some limitations. First, its retrospective design makes it especially susceptible to selection bias, as the final decision of performing or not a preoperatory amniocentesis, and subsequently a cervical cerclage, depended only on the clinical criteria of the attending physician. Second, given the sample size, it is difficult to establish with certainty whether the poor pregnancy outcome observed in patients with IAI/I is a consequence of the latter, or due to the lack of placement of a cervical cerclage. Also, given the small number of patients in the group that underwent an emergency cerclage without amniocentesis, it is difficult to establish proper comparisons among groups.

Conclusion

Patients with midtrimester cervical insufficiency and bulging fetal membranes have adverse pregnancy outcomes, and placement of a cervical cerclage is an effective therapy in those cases. However, a significant number of patients with cervical insufficiency and bulging fetal membranes have IAI/I, and its presence is associated with a poor prognosis. Therefore, in patients with demonstrated IAI/I, considering the potential maternal and fetal risks of placing a cervical cerclage and the lack of evidence of its benefits, we propose that this surgical procedure should not be recommended. In contrast, absence of IAI/I is associated with a better pregnancy outcome, and placement of a cervical cerclage should be strongly recommended in these cases. Preoperative amniocentesis is crucial to exclude IAI/I and plays a major role to select patients who are best candidates for an emergency cervical cerclage.

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