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Outcomes of physical examination-indicated cerclage in twin pregnancies with acute cervical insufficiency compared to singleton pregnancies

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Abstract

Objectives: To compare pregnancy outcomes of physical examination-indicated cerclage in twin pregnancies with acute cervical insufficiency with that of singletons.

Methods: This retrospective cohort study included 88 consecutive women (17 twins and 71 singletons) who had undergone physical examination-indicated cerclage because of acute cervical insufficiency (defined as painless cervical dilation with (1) prolapsed and/or visible membranes at the external cervical os on speculum examination and (2) a functional cervical length of zero on transvaginal ultrasound) between 16^{0/7} and 23^{6/7} weeks. The primary outcome measure was preterm delivery <34 weeks.

Results: (1) The frequency of preterm delivery <34 weeks was not significantly different between the two groups [twins, 56% (9/16) vs. singleton, 53% (37/70), $P > 0.999$]. (2) The perinatal mortality was 21% (7/34) in twins and 32% (23/71) in singletons. (3) The median gestational age at delivery for twin pregnancies was 31.0 weeks (IQR, 22.6–36.5 weeks), which was similar to that of singleton pregnancies (median 32.4 weeks; IQR 22.3–38.3 weeks). (4) There were no significant differences in preterm delivery before 28 and 32 weeks, interval from cerclage to delivery within 1, 2, 4 and 8 weeks and neonatal morbidities between the two groups.

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Conclusion: The obstetric and neonatal outcomes of physical examination-indicated cerclage in twin pregnancies were comparable to those in singleton pregnancies.

Keywords: Cervical insufficiency; physical examination-indicated cerclage; preterm birth; twins.

Introduction

Twin gestations have increased continuously and now account for about 3% of all live births, mostly due to the increased use of assisted reproductive technology [1]. Preterm birth in twin gestations is five times greater than in singleton gestations [1–3]. In 2015, 59.1% of twin pregnancies delivered before 37 weeks and 10.7% before 32 weeks, whereas in singleton pregnancies 7.8% delivered before 37 weeks and 1.2% before 32 weeks [1]. A higher rate of preterm birth in twin pregnancies is a major cause of increasing neonatal morbidity and mortality compared with singleton pregnancies.

Acute cervical insufficiency is a well-known cause of preterm birth. Acute cervical insufficiency, defined as painless cervical dilation in the mid-trimester, is estimated to account for 10–25% of all second-trimester pregnancy losses [4–6]. Moreover, cervical dilation with membrane exposure increases the risk of extreme preterm birth and chorioamnionitis [7, 8]. The overall rate of preterm birth in pregnancies complicated with acute cervical insufficiency has been reported to be as high as 90% [9–14]. Several studies have reported that the cervical length in multifetal pregnancies is significantly shorter than that in singleton pregnancies [15–18].

Cervical cerclage has become an acceptable treatment option for singleton gestations with acute cervical insufficiency [10, 19–23]. Recent retrospective studies have reported that cerclage may prolong pregnancy and improve neonatal outcomes in twin pregnancies with acute cervical insufficiency [4, 24, 25]. However, these studies have different indications for physical examination-indicated cerclage. In the largest study of twin pregnancies with

cervical dilatation diagnosed by digital examination, only 21% had membranes prolapsed beyond the external os [4]. The problem is that many of these women with visible fetal membranes can also be classified as having a short cervix in other studies. For example, Groom et al. [26] reported that fetal membranes were observed in 67% of women with a cervical length ≤ 10 mm and in 20% of those with a cervical length ≤ 20 mm. Recently, Berghella et al. [27] reported that cerclage in singletons without prior spontaneous preterm birth seems to be efficacious at cervical length < 10 mm. However, more studies are needed to determine the efficacy of ultrasound-indicated cerclage in twin pregnancies [28]. To exclude those who were classified as having a short cervix by other investigators, we planned to include only twins with the mother having a functional cervical length of zero and visible fetal membranes by speculum examination. The aim of this study was to evaluate the efficacy of physical examination-indicated cerclage in twin pregnancies and compare it to that of singletons in acute cervical insufficiency defined as a functional cervical length of zero and visible fetal membranes by speculum examination.

Materials and methods

Study design

A retrospective study of 88 consecutive women who had undergone physical examination-indicated cerclage after diagnosis of acute cervical insufficiency in our hospital from January 2005 to June 2015 was performed. Acute cervical insufficiency was defined as painless external os dilation with prolapsed and/or visible membranes on speculum examination and a functional cervical length of zero on ultrasound. The study population was divided into two groups: twin pregnancies and singleton pregnancies.

The specific inclusion criteria in this study were as follows: (1) all pregnancies with acute cervical insufficiency; (2) cerclage performed between 16^{0/7} and 23^{6/7} weeks' gestational age; (3) intact membranes; (4) the absence of regular uterine contractions; (5) no history of receiving prophylactic cerclage during the current pregnancy period and (6) no evidence of major congenital anomaly. Patients who had been diagnosed or suspected with clinical chorioamnionitis at the time of cerclage or who had been confirmed as one fetal demise before the procedure in twin pregnancies were excluded. The study protocol was approved by the Institutional Review Board of our institute.

Protocols of cerclage procedure

During the study period, physical examination-indicated cerclages were performed by a maternal-fetal medicine attending physician using a McDonald technique under spinal anesthesia. For some cases with membranes prolapsed out of the external os, amnioreduction was performed prior to cerclage placement to reduce tension of

the membranes and to allow holding the borders of the cervix. Pushing the surface of membranes by using intracervical Foley catheter balloon was applied for some cases with prolapsed membranes that were not easily retracted.

Tocolytics are not routinely used perioperatively. All patients received prophylactic perioperative antibiotics while the regimens and duration of use were decided at the discretion of the attending physician. After the procedure, patients were hospitalized for several days and then managed as outpatients with instructions on avoiding vigorous physical activities. Bed rest was not routinely recommended.

The outcomes of pregnancy and neonates

Data including the maternal and neonatal outcomes were collected. For some patients who had given birth at other hospitals, as many pregnancy and neonatal outcomes as possible were collected through individual telephone contacts to patients directly or to the attending physicians of the corresponding hospitals. Maternal characteristics included age, parity, and previous obstetric history such as term delivery, spontaneous preterm delivery before 37 weeks of gestation and mid-trimester fetal loss. The characteristics implicating degrees or conditions of acute cervical insufficiency for each patient were reviewed: gestational age at the time of cerclage, the size of visible membranes and the use of tocolytics and antibiotics.

The primary outcome measure was spontaneous preterm delivery before 34 weeks of gestation. Cerclage to delivery interval was analyzed by dividing into four categories as follows: within 1, 2, 4 and 8 weeks. The proportion of preterm delivery before 34 weeks, which is the primary outcome of the study, was compared between the two groups and the same analysis was performed for proportions of delivery before 28, 32 and 36 weeks.

To compare the neonatal outcomes between twin and singleton pregnancies, birthweight, Apgar scores, the rate of neonatal intensive care unit (NICU) admission, significant morbidity and neonatal deaths were analyzed. Neonatal morbidities included respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC) and intra-ventricular hemorrhage (IVH). Significant morbidity in this study was defined when one or more neonatal outcomes including RDS, BPD, NEC and IVH were diagnosed [29].

Statistical analysis

Continuous variables were compared using the Mann-Whitney *U* test; proportions were compared using Fisher's exact test. The Kaplan-Meier survival curves and log-rank tests were performed to compare the gestational age at delivery according to the plurality of gestation. Multivariable logistic regression was used for adjusting the variables confounding to the outcomes. A *P*-value < 0.05 was considered statistically significant. The analysis was performed by SPSS, version 22 (IBM SPSS Inc., Armonk, NY, USA).

Results

A total of 88 women were identified according to the inclusion criteria. Among them, 17 (19.1%) cases were twin

pregnancies and 71 (80.9%) were singletons. The baseline characteristics of the study population are presented in Table 1. There were significantly more nulliparous women in the twin group than in the singleton group [77% (13/17) vs. 44% (31/71), $P = 0.029$]. Except for parity, there were no significant differences in maternal age, history of previous spontaneous preterm delivery, history of prior mid-trimester loss, gestational age at cerclage and the size of visible membranes between the twin group and the singleton group. In the study population, 77 cases underwent trans-abdominal amniocentesis. The rate of positive culture and white blood cell count in amniotic fluid were comparable between twin and singleton pregnancies. There were no significant differences in the use of tocolytics, antibiotics

and the rate of antenatal steroids given between the two groups.

Table 2 shows pregnancy outcomes compared between twin and singleton pregnancies. There were no significant differences in gestational age at delivery and proportions of cerclage to delivery interval within 7 days, 2, 4 and 8 weeks. The rate of spontaneous preterm delivery before 28, 32, 34 and 36 weeks of gestation was comparable between the two groups. A comparison of the survival curves of the study population according to the groups based on gestational age at delivery is shown in Figure 1. The Kaplan-Meier survival curves show that there is no significant difference between singleton and twin pregnancies who underwent emergency cervical cerclage ($P = 0.738$).

Table 1: Demographic and clinical characteristics of the study population compared between twin and singleton pregnancies.

	Twin pregnancies (n = 17)	Singleton pregnancies (n = 71)	P-value
Maternal age (years)	31.0 (30.0–34.0)	32.0 (30.0–34.3)	0.753
Nulliparity	77% (13)	44% (31)	0.029
Previous term delivery	24% (4)	49% (35)	0.063
Previous spontaneous preterm delivery (<37 weeks)	6% (1)	11% (8)	>0.999
Prior mid-trimester loss	6% (1)	9% (6)	>0.999
Gestational age at cerclage (weeks)	20.7 (20.1–21.8)	21.4 (20.3–22.4)	0.300
Visible membrane size (cm)	4.0 (1.5–5.0)	3.0 (1.0–4.0)	0.064
Visible membrane size ≥ 4 cm ^a	59% (10)	33% (23/70)	0.057
Positive AF culture ^b	7.1% (1/14)	4.8% (3/63)	0.560
AF WBC (cells/mm ³) ^b	5 (2–35)	7 (2–10)	0.781
Use of tocolytics	59% (10)	47% (33)	0.425
Use of antibiotics	100% (17)	100% (71)	>0.999
Use of antenatal steroids ^c	41.7% (5/12)	31.9% (15/47)	0.518

AF = Amniotic fluid, WBC = white blood cell count. Data are median (interquartile range) or % (n). ^aOne case was excluded in this analysis because there was no record about the size of visible membranes. ^bSeventy-seven cases underwent trans-abdominal amniocentesis at the time of admission for cerclage operation. ^cIn this analysis, patients who had delivered before 24 weeks of gestation (n = 29) were excluded.

Table 2: Pregnancy outcomes compared between twin and singleton pregnancies.

	Twin pregnancies (n = 17)	Singleton pregnancies (n = 71)	P-value
Gestational age at delivery (weeks)	31.0 (24.1–36.5)	32.4 (22.3–38.3)	0.460
Cerclage to delivery interval (n/N) ^a			
<7 days	6% (1/17)	20% (14/70)	0.284
<2 weeks	12% (2/17)	24% (17/70)	0.342
<4 weeks	19% (3/16)	37% (26/70)	0.242
<8 weeks	44% (7/16)	43% (30/70)	>0.999
Preterm delivery (n/N) ^a			
<28 weeks	44% (7/16)	41% (29/70)	>0.999
<32 weeks	50% (8/16)	47% (33/70)	>0.999
<34 weeks	56% (9/16)	53% (37/70)	>0.999
<36 weeks	63% (10/16)	57% (40/70)	0.784

Data are median (interquartile range) or % (n). ^aData were analyzed until the last follow-ups for two cases that had given birth at other hospitals.

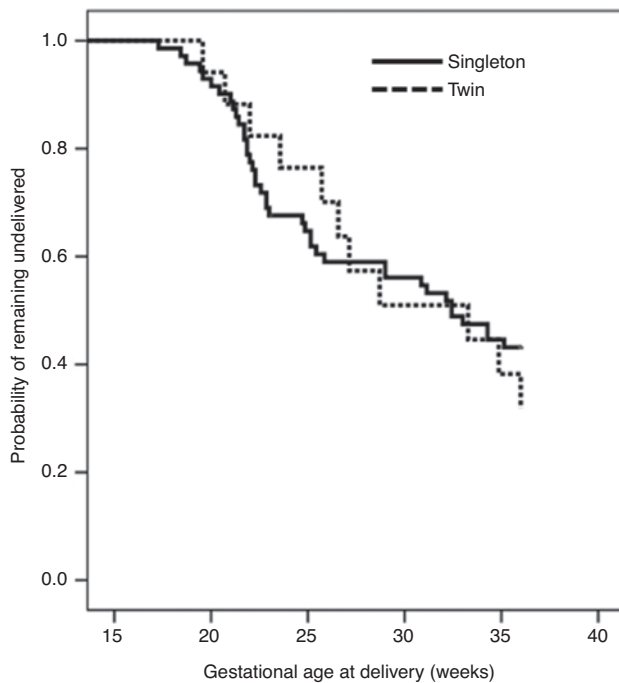


Figure 1: The Kaplan-Meier survival curves on gestational age at delivery after physical examination-indicated cerclage compared between twin and singleton pregnancies [median gestational age at delivery, 31.0 weeks (interquartile range, 24.1–36.5 weeks) in twin pregnancies vs. 32.4 weeks (interquartile range 22.3–38.3 weeks) in singletons, $P=0.738$].

The neonatal outcomes compared between the two groups are revealed in Table 3. Among a total of 105 neonates (34 twins and 71 singletons), 30 cases expired

within 24 h of birth. There were no significant differences in birthweight, Apgar scores at 1 min and 5 min, neonatal death rates, the rate of admission to NICU and neonatal morbidities. The overall perinatal mortality of the study population was 29.5%. The survival rate of twins was slightly higher than that of singletons, but the difference did not reach statistical significance (79% vs. 66%, $P=0.180$).

Table 4 shows the characteristics analyzed to determine their association with the spontaneous preterm delivery before 34 weeks, which is the primary outcome of this study. To evaluate confounding factors, the study population was divided into two groups based on whether the gestational age at delivery was before or after 34 weeks of gestation. The proportion of previous term delivery history was significantly higher in the group with preterm delivery at or after 34 weeks of gestation than the other with preterm delivery before 34 weeks (63% vs. 30%, $P=0.005$). A twin gestation itself was found to be not associated with the outcome. The group with preterm delivery before 34 weeks had significantly lower gestational age at cerclage (20.7 vs. 21.4, $P=0.010$) and larger size of visible membranes (4.0 vs. 1.5, $P=0.001$).

Multivariable logistic regression analysis was performed to evaluate the association of risk factors to the preterm delivery before 28 and 34 weeks of gestation (Table 5). A twin gestation was not associated with an increased odds ratio (OR) for both preterm delivery before 28 and 34 weeks [OR, 0.489; 95% confidence interval (CI), 0.121–1.978 and OR, 0.540; 95% CI, 0.141–2.063,

Table 3: Neonatal outcomes compared between twin and singleton pregnancies.

	Twin pregnancies (n = 34)	Singleton pregnancies (n = 71)	P-value
Birthweight (g)	1920 (770–2579)	2085 (492–3241)	0.413
Apgar score 1 min <7 ^a	59% (16/27)	53% (31/58)	0.647
Apgar score 5 min <7 ^a	44% (12/27)	53% (31/58)	0.490
Deaths (n/N)			
Shortly after birth, <1 day	21% (7/34)	32% (23/71)	0.253
Neonatal period, <28 days	21% (7/34)	34% (24/71)	0.180
Admission to NICU ^b	52% (13/25)	33% (16/48)	0.138
Significant morbidity ^{b,c}	29% (7/24)	18% (8/44)	0.364
Neonatal death and/or any significant morbidity ^c	45% (14/31)	46% (31/67)	>0.999
Survival rate	79% (27/34)	66% (47/71)	0.180

Data are median (interquartile range) or % (n). NICU = Neonatal intensive care unit. ^aTwenty cases were excluded for the analysis because they had given birth at other hospitals and Apgar scores were impossible to identify through telephone contacts. ^bThirty neonates who expired immediately after birth in the delivery room were excluded for the analysis. ^cSeven cases were excluded for the analysis because they had given birth at other hospitals and specific neonatal outcomes including NICU admission and morbidities were impossible to identify through telephone contacts.

Table 4: The clinical characteristics analyzed to determine their association with the spontaneous preterm delivery before 34 weeks.

	Preterm delivery <34 weeks (n=46)	Preterm delivery ≥34 weeks (n=40)	P-value
Maternal age (years)	32.0 (30.0–34.5)	32.0 (30.0–34.8)	0.767
Previous term delivery	30% (14)	63% (25)	0.005
Previous spontaneous preterm delivery (<37 weeks)	9% (4)	13% (5)	0.728
Twin gestations	20% (9)	18% (7)	>0.999
Gestational age at cerclage (weeks)	20.7 (19.4–21.7)	21.4 (20.7–22.7)	0.010
Visible membrane size (cm)	4.0 (2.0–4.0)	1.5 (1.0–3.0)	0.001
Visible membrane size >4 cm ^a	51% (23/45)	23% (9)	0.008
Use of tocolytics	54% (25)	43% (17)	0.289
Use of antibiotics	100% (46)	100% (40)	>0.999

Data are median (interquartile range) or % (n). ^aOne case was excluded in this analysis because there was no record about the size of visible membranes.

Table 5: Multivariable analyses of factors associated with preterm delivery before 28 weeks and 34 weeks.

	Preterm delivery <28 weeks			Preterm delivery <34 weeks		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Gestational age at cerclage (weeks)	0.657	0.460–0.937	0.020	0.721	0.510–1.018	0.063
The size of visible membranes (cm)	1.553	1.148–2.101	0.004	1.389	1.046–1.843	0.023
Twin gestations	0.489	0.121–1.978	0.316	0.540	0.141–2.063	0.367
History of previous term delivery	0.481	0.166–1.392	0.177	0.278	0.101–0.763	0.013

CI = Confidence interval.

respectively]. The size of visible membranes was found to be independently associated with preterm delivery before 28 and 34 weeks (OR, 1.553; 95% CI, 1.148–2.101 for preterm delivery before 28 weeks and OR 1.389; 95% CI, 1.046–1.843 for preterm delivery before 34 weeks). In addition, previous history of term delivery was independently associated with preterm delivery before 34 weeks (OR, 0.278; 95% CI, 0.101–0.763) and gestational age at cerclage was associated with preterm delivery before 28 weeks (OR, 0.657; 95% CI, 0.460–0.937).

Discussion

Principle findings of the study

(1) The frequency of preterm delivery before 34 weeks of gestation was not significantly different between twin and singleton pregnancies [twins, 56% (9/16) vs. singleton, 53% (37/70), $P = \text{NS} > 0.999$]. (2) The perinatal mortality was 21% (7/34) in twin pregnancies and 32% (23/71) in singletons. (3) There were no significant differences in preterm delivery before 28, 32, 34 and 36 weeks of gestation, interval from cerclage to delivery and the neonatal

outcomes between the two groups. (4) Multivariate analysis showed that a lower gestational age at cerclage and a larger size of visible membranes were independently associated with a higher risk of preterm delivery before 34 weeks of gestation; however, a twin gestation itself was not a risk factor.

Concerns about physical examination-indicated cerclage in twin gestations

In the current study, most obstetric and neonatal outcomes were comparable between twin and singleton pregnancies. For patients who presented with acute cervical insufficiency, physical examination-indicated cerclage has been known to be beneficial for prolongation of the pregnancy period and improvement of clinical outcomes in singletons. Therefore, the similar outcomes of twin gestations who receive physical examination-indicated cerclage compared to singletons likely suggest that the cerclage procedure for women with acute cervical insufficiency in twin pregnancies could be an effective treatment option.

However, there is a paucity of data on the effectiveness of cerclage in twin pregnancies with acute

cervical insufficiency. Recently, a few retrospective studies reported that physical examination-indicated cerclage can be associated with a favorable outcome in twin pregnancies with acute cervical insufficiency [4, 24, 25, 30]. The neonatal survival rate was 70% (7/10) [24], 72.4% (55/76) [30] and 83.3% (10/12) [25]. The gestational age at delivery was 31.2 weeks [30], 31.9 weeks [4] and 33.5 weeks [25]. These findings are in keeping with those of the current study in which the survival rate was 79% and the median gestational age at delivery was 31.0 weeks.

On the contrary, the indications for physical examination-indicated cerclage were different among the above studies. The definitions of acute cervical insufficiency were a dilated cervix on examination or membranes visible at the external cervical os on speculum examination in the study of Rebarber et al. [25], cervical dilation diagnosed by digital examination in the study of Miller et al. [4], cervical dilation of the internal os ≥ 1 cm or prolapsed membranes up to the external os [30] and easily visualized membranes through a dilated internal cervical os in the study of Aguilera et al. [24]. In the current study, acute cervical insufficiency was defined as painless cervical dilation with prolapsed and/or visible membranes at the external cervical os on speculum examination [31–33] and a functional cervical length of zero not to confuse with short cervical length.

The largest study reported that outcomes of physical examination-indicated cerclage in twin gestations had similar obstetric outcomes compared to singleton gestations (104 twin pregnancies and 338 singletons) [4]. However, in their study population, the degree of cervical dilation measured by digital examination was 1–2.5 cm with a median value of 1.5 cm, which could be classified as a short cervix by other investigators. Compared to that, the current study was performed only in cases confirmed to show external os dilation with prolapsed and/or visible membranes on speculum examination and a functional cervical length of zero. Membranes bulging into vaginal canal were presented in more than half [58.0% (51/88)] of the study population.

Strong evidence suggests that cerclage is not beneficial for prevention of preterm birth for a single indication of the following: twin gestation [34], history of preterm delivery [35, 36] and short cervical length [28]. In the meta-analysis by Berghella et al. [28], a trend toward higher perinatal mortality was also found in twin pregnancies with short cervical length. These findings suggest that cerclage may be beneficial only in twin pregnancies with advanced cervical insufficiency. Therefore, the indications for physical examination-indicated cerclage need to be thoroughly

reviewed when establishing guidelines on cerclage in twin pregnancies with acute cervical insufficiency.

Factors affecting interval to delivery after cerclage in acute cervical insufficiency patients

We performed the multivariable regression analysis of several risk factors to determine whether a twin gestation was an independent risk factor associated with preterm delivery. A lower gestational age at cerclage and a larger size of visible membranes were independently associated with a higher risk of preterm delivery, however, a twin gestation itself was not found to be a risk factor. Interestingly, the history of previous term delivery showed a significantly lower rate of preterm delivery before 34 weeks with an OR=0.28. In twin gestations, the median gestational age of delivery for four cases with a history of previous term delivery was higher than that of 13 cases who were nulliparous, although the difference did not reach statistical significance probably due to the small sample size (36.2 weeks vs. 28.2 weeks, $P=0.138$). The result might be helpful for counseling twin pregnancies through individualization according to parity and obstetric history.

Limitations

Physical examination-indicated cerclage for acute cervical insufficiency is a hard topic for a dedicated randomized study design as a physician facing patients presenting with a dilated cervix cannot easily decide to do nothing for the cases assigned as a control group. Setting this ethical difficulty aside, another obstacle for research is that the clinical outcomes of physical examination-indicated cerclage more largely depend on the skills and techniques of attending surgeons than on history-indicated cerclage or ultrasound-indicated cerclage. Moreover, cerclage in twin gestations likely leads to more confusing results because it is associated with an increase in the rate of preterm delivery in those with a short cervical length [28].

The limitation of this study is the relatively small sample size. However, we used the most restrictive definition not to include patients who were classified as short cervical length in other studies. In addition, still the retrospective nature of the study design is an inevitable limitation. Besides the variables analyzed in this study, other hidden factors could have influenced the outcomes of cerclage. Another limitation is that comparing with singleton

pregnancies is an indirect method for evaluation of the effectiveness of cerclage in twin pregnancies.

Clinical implications

The obstetric and neonatal outcomes of physical examination-indicated cerclage in twin pregnancies were comparable to those in singleton pregnancies. It indirectly supports the view that cerclage may be beneficial for prolongation of pregnancy and neonatal outcome in the twin pregnancy with a dilated internal os and visible fetal membranes. A randomized controlled study may determine the effectiveness of cerclage in twin pregnancies with acute cervical insufficiency. However, it would be very difficult to perform a randomized controlled study comparing cerclage to conservative management in twin pregnancies with acute cervical insufficiency because of ethical issues and rarity of the patient. We hope that the findings of our study could be helpful in the counseling of twin pregnancies with acute cervical insufficiency.

Author's statement

Conflict of interest: Authors state no conflict of interest.

Material and methods: Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research related to human subject use has complied with all the relevant national regulations, and institutional policies, and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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