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Randomized trial of ultrasound-indicated cerclage in singleton women without lower genital tract inflammation

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Abstract

Aim: This is the first report of a randomized trial of cerclage on pure cervical shortening without vaginosis or cervicitis. The objective of our multicenter randomized controlled trial was to assess the benefits of ultrasound-indicated cervical cerclage in the mid-trimester to prevent preterm birth in women who have no signs of infection or inflammation of the lower genital tract.

Material and Methods: Women with a short cervical length < 25 mm between 16 and 26 weeks of gestation were randomly assigned to receive a Shirodkar cerclage, McDonald cerclage, or bedrest (no cerclage). Before being randomly assigned to one of the three groups, all women were screened for infection/inflammation of the lower genital tract; those with positive results were excluded from the study. The ratio of preterm delivery as a primary end-point was evaluated in the groups.

Results: A total of 106 singleton patients with a short cervical length were assessed for study eligibility; 106 patients were randomized to the three treatment options. Ultimately, 98 patients (in the Shirodkar [n = 34], McDonald [n = 34] and bedrest [n = 30] groups) were analyzed. No differences in preterm delivery or perinatal outcomes were found between the three groups. Significantly fewer patients in the Shirodkar group required hospitalization for treatment of threatened preterm labor when compared to patients in the bedrest group.

Conclusion: For women with a short cervical length < 25 mm between 16 and 26 weeks of gestation, Shirodkar cerclage might be considered to reduce the occurrence of threatened preterm labor.

Key words: cervical shortening, randomized trial, transvaginal ultrasound cervical cerclage.

Introduction

Preterm birth (PTB) is a major cause of perinatal morbidity and mortality. A short cervical length on transvaginal ultrasound examination in the mid-trimester is one of the best predictors of PTB.[1–5] When cervical shortening is diagnosed, a cervical cerclage has been proposed to prevent PTB;[6–8] however, several randomized trials have not supported this practice.[9–11] Recently, a patient-level meta-analysis[12] of five randomized trials[7,9–11,13] reported that a cerclage is an effective practice in singleton pregnancies, and it is especially beneficial in women

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who have had a prior PTB. Shirodkar[14] and McDonald have described two commonly performed cerclage procedures,[14] and a few studies comparing their efficacy have reported conflicting results.[15–18] These findings emphasize the need for further study regarding appropriate candidate selection and the comparison of these procedures for a cervical cerclage.[19,20] Furthermore, Sakai *et al*.[21] reported that elevation of cervical mucus IL-8 concentration could serve as a marker of cervical inflammation, and this situation cerclage may increase the rate of preterm delivery. Berghella[12,22] showed that in pregnant women with previous PTB and cervical length < 25 mm, cerclage prevented premature birth and reduced perinatal mortality and morbidity composite. He concluded that women with prior PTB and short cervix should not undergo cerclage. Nevertheless, these randomized trials were published mainly from the USA. Second, these randomized trails did not mention the existence of cervical inflammation. We also mentioned that the rate of PTB in the USA is two times that in Japan. Regardless of the differences in the health insurance systems and the management of preterm labor between Japan and the USA, this is the most important point. These facts have not been mentioned or discussed in recent randomized trials concerning the efficacy of cervical cerclage in prevention of PTB. Thus, we aimed to carry out this study in Japan, where the rate of PTB is half that in the USA. Additionally, in Japan, progesterone (gel or vaginal tablet) has not been commercially sold and is not popular for patients with high risk of PTB. Consequently, it is extremely difficult to carry out a multicenter, randomized, controlled trial to compare the benefits of cerclage and progesterone.

This is a reasonable suggestion because invasive procedures on a cervix with inflammation may induce uterine contractions by stimulating the prostaglandin cascade. Therefore, the objective of our multicenter, randomized, controlled trial was to assess the benefits of ultrasound-indicated cervical cerclage in the midtrimester to prevent PTB in women who have no signs of infection or inflammation of the lower genital tract. Another objective was to compare the efficacy of the Shirodkar cerclage to the McDonald procedure for the prevention of PTB.

Methods

Study design and setting

The planning and execution of this multicenter randomized controlled trial (RCT) was officially approved and supported by the Ministry of Health, Labor and Welfare from 2004 to 2009. This RCT was performed by a consortium of 60 tertiary centers of the Japanese Society of Preterm birth Prevention (JOPP). The study was approved by the institutional review board of each participating center, and all participants provided written informed consent. The JOPP Data Safety Monitoring Board also reviewed and approved the study. As no significant difference was observed in primary end-point at midterm analysis, recruitment of the patients was performed by a consortium of 60 tertiary centers of the JOPP between January 2007 and November 2011. This clinical trial was registered on the University hospital Medical Information Network (UMIN) in Japan, an acceptable registry of International Committee of Medical Journal Editors (ICMJE). (UMIN000001870).

Ethical considerations

Before beginning the research, a summary of the protocol was explained to each patient. It was explained that no disadvantage was associated with nonparticipation in this research, and that participation could be discontinued at any time. The participants were assured that at any stage in which a clear statistical difference in the incidence rate of preterm delivery would appear in any group, the group in which rates of preterm delivery were clearly higher would have that protocol discontinued. In each test center participating in this study, the patients were enrolled and assigned to treatment via an Internet homepage specifically designated for this research. Multilayer passwords were established to maximize protection against any leakage of personal information.

Study participants

All women were routinely offered an ultrasound examination between 8 weeks and 11^{+6} weeks of gestation for pregnancy dating. As part of this study, all patients between the gestational ages of 16 and 26 weeks underwent a transvaginal ultrasound scan to measure cervical length in order to screen for the risk of PTB. Specifics of the ultrasound evaluation used in this study were as previously described.[5] Briefly, the cervical length was measured along a closed endocervical canal at each visit between 16 and 26 gestational weeks. Pressure on the lower uterine segment was also applied for 30 s as a provocative maneuver, and each scan included an evaluation period of at least 3 min to detect spontaneously occurring cervical shortening. The shortest cervical length for each examination that clearly displayed the internal and external cervical os with equivalent thickness of the anterior and posterior cervix was recorded as the

cervical length, regardless of whether the measurement was obtained with pressure or was the result of spontaneous dynamic shortening.[23]

Women with a cervical length of 25 mm or less were invited to participate in the randomized study. Exclusion criteria comprised the following: fetal abnormalities; regular uterine contractions; rupture of membranes; planned cerclage due to a clinical diagnosis of cervical insufficiency; and clinically significant maternal–fetal complications that would increase the risk of an indicated PTB and potentially confound the primary study outcome. Women with a dilated cervix during screening were also excluded; however, women who had received a cerclage in a prior pregnancy were still eligible for inclusion.

After informed written consent was obtained, all women who met the inclusion criteria and desired to participate in the study were screened for infection or inflammation of the lower genital tract. The vaginal secretions were obtained via a sterile swab for cultures and the presence of bacterial vaginosis. Bacterial vaginosis was detected using a FemExam kit (Cooper Surgical).[24–30] The FemExam kit contains a colorimetric pH indicator and colorimetric amines tests for use in the characterization of a vaginal fluid sample as follows: (i) a pH test that differentiates vaginal fluid pH $<$ pH 4.7 from vaginal fluid pH $\geq$ 4.7; and (ii) a test that detects alkali volatilizable amines in vaginal fluid. The cervical secretions were also taken for granulocyte elastase assessment. Granulocyte elastase is a biological marker for inflammation.[29–31] An increased level of granulocyte elastase in cervical secretions was an independent predictive factor for PTB.[30–33] Elastase concentration was measured using a kit according to the manufacturer's instructions (Granulocyte Elastase ELISA). Briefly, supernatants were added to a 96-well microtiter plate coated with antibodies (antihuman elastase mouse monoclonal antibody) specific to granulocyte elastase. After incubation, the wells were washed. Peroxidase-labeled antibodies (antihuman elastase sheep polyclonal antibody) were then added. After incubation, the wells were washed. Substrate (H2O2) and o-phenylenediammonium dichloride were added, and color development was halted with a H2SO4 solution. The color intensity of the reaction mixture was measured with a photometer. The cut-off value was 1.6 mg/L for granulocyte elastase per the manufacturer's instruction and the literature.[34] A qualitative positive result for elastase (kit for detection of granulocytic elastase in cervical mucus) was used for the detection of cervicitis. A secretion that yielded a positive FemExam kit or granulocyte elastase concentration $>$ 1.6 mg/L was defined as a lower genital tract infection/inflammation; these women were excluded from the protocol. We also performed another RCT study on women with short cervices and lower genital tract infection/inflammation. This manuscript is under development.

Primary end-point, target sample size and rationale

The primary end-point indicated below will be evaluated in the groups receiving cervical cerclage (Shirodkar cerclage group and McDonald cerclage group) versus the bedrest group, using gestational age at delivery.

For a comparison of groups receiving surgery and bedrest therapy, no highly reliable or useable database in Japan is available relating to preterm delivery rates achieved with bedrest therapy in patients (pregnant women) with a background similar to the patients in this study. Accordingly, based on the experience of physicians participating in this study, the assumption was made that 10–20% of preterm deliveries would occur at $<$33 weeks in the bedrest group. Based on analogies to drug treatment evaluations, a clinically significant decrease in the risk of preterm delivery would be 33–50%, and the numbers-needed-to-treat would be established at 15–20%. Thus, with a level of significance of $\alpha = 0.05$ (two-tailed) for tests used to compare the two groups associated with the primary end-point (groups receiving surgical procedures, i.e., the Shirodkar cerclage group and the McDonald cerclage group) versus the bedrest group, the required numbers of patients was calculated per group, with the power of the test at $1\text{-}\beta = 0.80$. At the same time, in view of estimates of discontinuations/withdrawals of 5–10%, and given the potential for recruiting patients, the decision was made to establish a target sample size of each group.

Randomization

Enrolled women were randomly assigned to receive a Shirodkar cerclage, a McDonald cerclage, or no cerclage. The randomization sequence was computer-generated in balanced block multiples. The factors of this randomization included maternal and gestational age at participation, parity, severity of cervical shortening, and history of previous preterm delivery. For this study, the JOPP research team established and hosted a secure page on the UMIN website that was used to randomize subjects into the groups. All communication between participating centers and the JOPP research team was encrypted. Staff responsible for recruitment and randomization accessed the website through a password-protected web portal. Only eight patients were excluded after randomization. The reasons for exclusion were

patient request (n = 3) and insufficient data due to patient relocation after hospital discharge (n = 5).

Enrolled patients were then hospitalized (Fig. 1). After hospitalization, the patients were checked for subclinical infection based on the elastase level of the cervical mucus and the presence of bacterial vaginosis. The patients with positive results for subclinical infection were excluded from this study and received alternative treatment. The patients without subclinical infection were divided into the following three groups: Group A, Shirodkar cerclage; Group B, McDonald cerclage; and Group C, bedrest without cerclage.

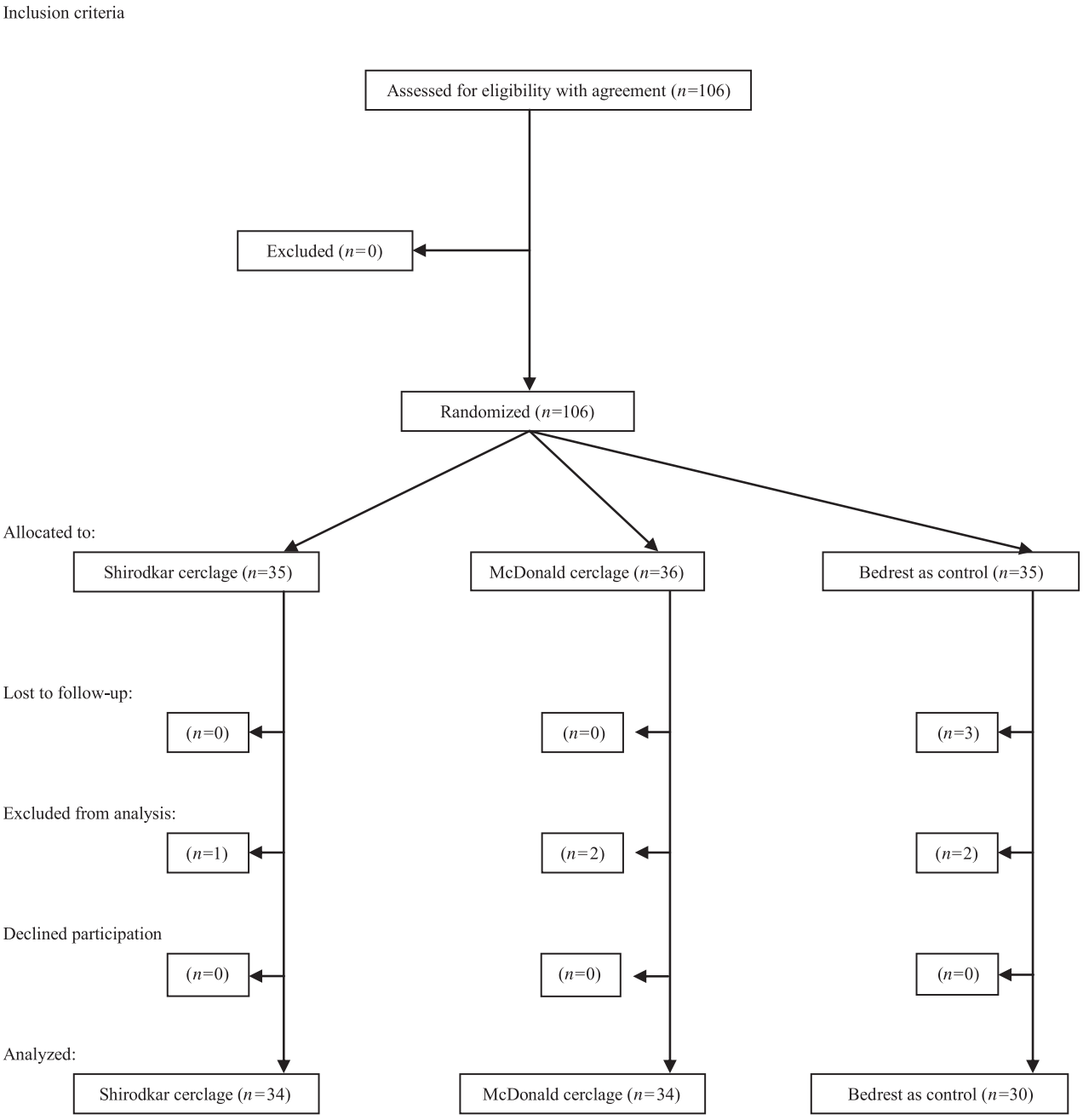

Figure 1 Flow diagram of progress through the phases of this trial.

Intervention and follow-up

All consenting women were treated as inpatients with bedrest. The women in all three groups were discharged from the hospital after 2 weeks from operation (Group A and B) or admission (Group C). Outpatient treatment involved bi- or tri-weekly ultrasound evaluation of the lower uterine segment, instruction regarding the signs and symptoms of preterm labor, and routine antenatal care. In the absence of pregnancy complications requiring earlier delivery (e.g., premature rupture of membranes, labor, or hemorrhage), the cerclage suture was removed at 37 weeks of gestation.

All participants were otherwise treated according to standard obstetric indications; the route and timing of delivery was at the discretion of the attending physician in each center.

Rescue arm and procedures

When any of the following conditions occur, the investigator or sub-investigator should make the appropriate diagnosis based on the written procedures and take appropriate medical action. If these conditions suggest an elevated risk of preterm delivery, the patient should be transferred to the rescue arm. Treatment in the rescue arm will be identical for Groups A, B, and C:

1. Bulging membranes
   i. Bedrest
   ii. Tocolysis: Treatment should focus on administration of ritodrine hydrochloride; however, if this is not possible, consider using magnesium sulfate.
   iii. Steroids: Use when preterm delivery is expected at less than 34 weeks of gestation.In cases in which chorioamnionitis can be ruled out, when used for potential effects on maturation of fetal lungs, cardiovascular system, or digestive system, administer 12 mg of betamethasone by intramuscular injection, two times with a 24-h interval. However, repeat administration is not allowed.
   iv. Vaginal douche or cerclage
2. Preterm premature rupture of membranes[35,36]
   i. Perform laboratory cultures of bacteria using samples taken from vaginal discharge or by amniocentesis.
   ii. Antibiotic administration: Administer ampicillin (ABPC) at 2 g/day prophylactically until sensitivity results from laboratory cultures of bacteria from vaginal discharge or amniocentesis are obtained. Effective antibiotics are administrated after the sensitivity results are obtained.
   iii. Tocolysis: As mentioned above.
   iv. Steroids: As mentioned above.
3. Chorioamnionitis (CAM)[37,38]
   i. Antibiotic administration: As mentioned above.
   ii. Steroids: As mentioned above.
   iii. When maternal chorioamnionitis or non-reassuring fetal status is diagnosed, the patient should be delivered.
4. Inability to suppress uterine contractions
   i. Tocolysis; As mentioned above.
   ii. Response
      i. At less than 22 weeks of gestation: While respecting the desires of the patient, decide whether to continue or discontinue the pregnancy based on fully informed patient consent.
      ii. After 22 weeks of gestation: From week 22 up to week 25^{+6} of gestation, follow the treatment guidelines of the medical center while respecting the desires of the patient. From week 26 until CAM diagnosis, use tocolysis in an attempt to extend the pregnancy.
   iii. Steroids: As mentioned above.
   iv. When maternal chorioamnionitis or non-reassuring fetal status is diagnosed, the patient should be delivered.

Assessment of outcome and statistical analysis

Categorical variables were analyzed with the χ^2-test or Mantel–Haenszel test of trend, while continuous variables were compared using a Wilcoxon rank sum test. Differences between the groups were assessed by Dunnett analysis and Tukey's HSD analysis. Differences in time to birth were assessed by Kaplan–Meier curves and the log–rank test. Analysis was performed using JMP 10.0.

Results

A flow diagram of the participants is presented in Figure 1. None of these women were included in previous publications. Of 118 women, 106 patients (89.8%) were singleton gestations. A total of 38 patients were allocated for a Shirodkar cerclage; 40 were designated for a McDonald cerclage; and 40 were assigned to bedrest. Three patients in the bedrest group were lost to follow-up due to relocation. One patient in the Shirodkar group, two in the McDonald group, and two in the bedrest

group were excluded due to data loss; therefore, data from 37, 38, and 35 patients, respectively, were included for analysis.

Table 1 presents the demographic characteristics, obstetrical histories, and gynecologic histories of the women in the three groups. No significant differences were observed in these characteristics between groups. It was highly important that the pregnant women in this series had a low rate of previous PTB (14.3%). Table 2 presents the clinical characteristics and the pregnancy outcomes of the Shirodkar cerclage, McDonald cerclage, and bedrest groups. Mean cervical length at the initiation of the study (the time of randomization) and mean gestational age at the time of this measurement were comparable for three groups in this analysis. Cerclages were removed at a mean gestational age of 36.5 weeks. No differences were observed between the three groups in the rate of preterm delivery before 28, 30, 32, 34 and 37 weeks of gestation. No significant differences were seen between groups in gestational age at delivery, duration between admission and delivery, birthweight, neonatal survival, Apgar Score < 7, and number of operable deliveries or cesarean sections. The only statically significant difference found was in the number of cases moved into the rescue arm. The Shirodkar group had significantly fewer rescue arm cases than the bedrest group ($P = 0.019$).

Figure 2 presents survival curves of women who remained undelivered across gestational age (weeks). No significant differences between the three groups were observed. Figure 3, which presents survival curves of women who remained undelivered until term after cerclage, also shows no significant differences between the three groups.

Discussion

To the best of our knowledge, this is the first report of a randomized trial of cerclage on pure cervical shortening without vaginosis or cervicitis. The objective of our multicenter randomized controlled trial was to assess the benefits of ultrasound-indicated cervical cerclage in the mid-trimester to prevent PTB in women who had no signs of infection or inflammation of the lower genital tract. On 3 February 2011, the US Food and Drug Administration (FDA) approved the use of progesterone supplementation (hydroxyprogesterone caproate) during pregnancy to reduce the risk of recurrent PTB in women with a history of at least one prior spontaneous preterm delivery.[39] This is the first time that the FDA has approved a medication for the prevention of PTB, and represents the first approval of a drug specifically for use in pregnancy in almost 15 years in the USA. We also mentioned that the rate of PTB in the USA is two times of that of Japan. Regardless of the difference of the populations, the health insurance systems and the management of preterm labor between Japan and the USA, this is the most important point. These facts have not been mentioned or discussed in recent randomized trials concerning the efficacy of progesterone and cervical cerclage in the prevention of PTB. Concerning these backgrounds for progesterone, the Japanese government has not allowed physicians to use progesterone to prevent preterm delivery in Japan. Thus, we conducted this study comparing the benefits of ultrasound-indicated cervical cerclage in the mid-trimester to prevent PTB in women who had no signs of infection or inflammation of the lower genital tract. The fact that the number of cases moved into rescue the arm in the Shirodkar group was significantly lower than that in the bedrest group provides us with useful clinical information.

Iams *et al*.[1] measured cervical length at about 24 weeks' gestation using transvaginal ultrasonography; they reported high rates of preterm delivery in patients with short cervices. They also found that preterm delivery rates increased with the severity of cervical shortness. Subsequently, numerous reports have described

Table 1 Demographic characteristics

Characteristic	Shirodkar cerclage ($n = 34$)	*P*-value	McDonald cerclage ($n = 34$)	*P*-value	Bedrest ($n = 30$)
Age (years)	33.4 ± 4.5	NS	33.2 ± 4.9	NS	33.9 ± 3.6
Smoking (*n*)	1 (2.9%)	NS	2 (5.9%)	NS	1 (3.0%)
Alcohol (*n*)	0	NS	0	NS	0
History of PTB	4 (11.8%)	NS	5 (14.7%)	NS	5 (16.7%)
History of previous abortion	7 (20.6%)	NS	7(20.6%)	NS	8 (26.6%)
History of previous cerclage	1 (2.9%)	NS	2 (5.9%)	NS	1 (3.0%)

Data are mean ± standard deviation or *n* (%). NS, not significant; PTB, preterm birth.

Table 2 Clinical characteristics and pregnancy outcomes of women in the cerclage and bedrest groups

Characteristic	Shirodkar cerclage (n = 34)	P-value	McDonald cerclage (n = 34)	P-value	Bedrest (n = 33)
Gestational age at measurement	24.6 ± 2.8	0.61	24.6 ± 2.9	0.65	24.0 ± 3.2
Cervical length before randomization	18.3 ± 5.0	0.30	16.9 ± 4.5	0.91	16.4 ± 5.9
Maternal height	158.3 ± 4.7	0.35	158.7 ± 6.0	0.21	156.4 ± 5.8
Maternal bodyweight	58.1 ± 10.2	0.97	56.8 ± 10.0	0.85	55.5 ± 10.8
Gestational age at delivery	37.8 ± 2.5	0.45	36.7 ± 4.3	0.99	36.7 ± 4.6
Duration between randomization and delivery	13.2 ± 4.0	0.88	12.2 ± 4.3	0.84	12.7 ± 4.5
Birthweight	2693 ± 490	0.97	2574 ± 768	0.85	2717 ± 783
Preterm delivery < 28 weeks	0	NS	0	NS	0
Preterm delivery < 30 weeks	1 (2.9%)	0.76	2 (5.9%)	0.99	2 (6.1%)
Preterm delivery < 32 weeks	1 (2.9%)	0.79	6 (17.6%)	0.90	4 (12.1%)
Preterm delivery < 34 weeks	1 (2.9%)	0.34	6 (17.6%)	0.78	4 (12.1%)
Preterm delivery < 37 weeks	7 (20.0%)	0.50	11 (32.4%)	0.99	10 (30.3%)
Neonatal survival	0	0.56	1 (2.6%)	0.99	1 (5.7%)
Apgar score < 7	1 (2.9%)	0.99	2 (5.9%)	0.82	1(5.7%)
Compound delivery	3 (8.6%)	0.62	8 (23.5%)	0.57	6 (18.2%)
Rescue procedures	4 (11.4%)	0.019†	7 (20.6%)	0.13	12 (36.4%)

†Dunnett analysis *vs* control.

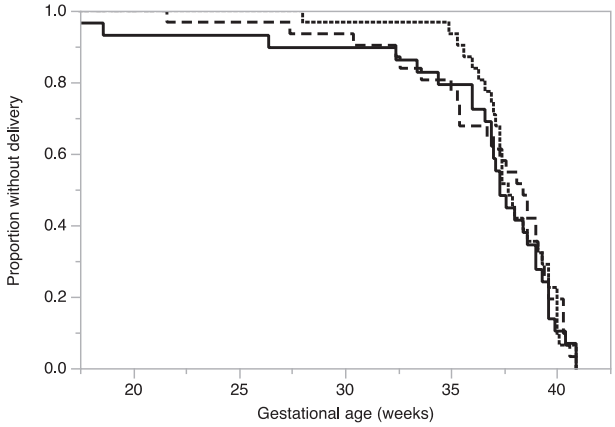

Figure 2 Proportion of women who remained undelivered by gestational age. Shirodkar cerclage (n = 34), McDonald cerclage (n = 34), bedrest (Control) (n = 30). Kaplan–Meier survival curves indicating the proportions of women in the cerclage and non-cerclage groups who did not experience preterm birth.

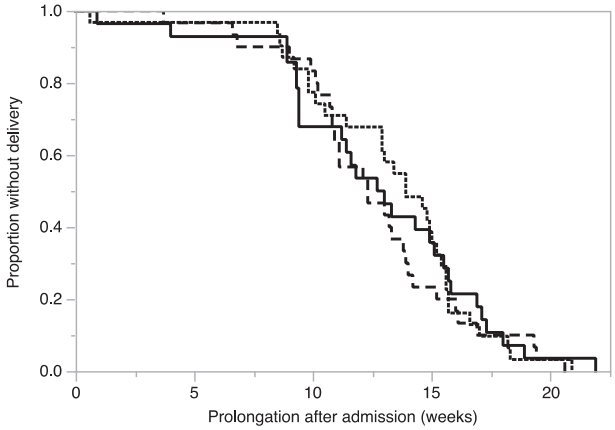

Figure 3 Proportion of women who remained undelivered by gestational age after admission. Shirodkar cerclage (n = 34), McDonald cerclage (n = 34), bedrest (n = 30). Kaplan–Meier survival curves indicating proportions of women in the cerclage and non-cerclage groups who did not experience preterm birth (log–rank test; P = 0.027).

relationships between cervical length during the second trimester and preterm delivery rate.[2–5,10,40] Thus, cervical shortness has been found to be a very sensitive indicator for preterm delivery. The cervix also provides a protective mechanism to prevent vaginal infections from ascending into the uterus. A short cervix physically facilitates ascending vaginal or cervical infection or inflammation; thus, it is considered to be a factor contributing to preterm delivery. If inflammation ascends up the cervical canal, cervical maturation progresses, the force maintaining the fetus weakens, the cervical os dilates and the cervix shortens. As a result, inflammation of the cervix is regarded to be a factor in preterm delivery. Therefore, whether or not inflammation of the lower

genital tract exists can affect the results of cervical cerclage in women with short cervices. A recent report from the Cochrane collaboration[41] also reported that cerclage, including the Shirodkar and McDonald procedures, did not provide any benefit to perinatal results. However, they did not mention the presence of cervical inflammation. That was the reason why we planned this trial. Apart from this study, we also planned another trial on patients with cervical shortening and vaginosis or cervical inflammation. This manuscript is under development.

From our results, even excluding the influence of infection or inflammation of the lower genital tract, we did not observe statistically significant differences between the Shirodkar cerclage, McDonald cerclage, and bedrest groups in regards to the prevention of birth before a gestational age of 35 weeks. However, we did find some benefit for pregnancy prolongation in the Shirodkar group after we discovered that short cervices moved the patients into the rescue arm. Thus, it can be noted that Shirodkar cerclage may reduce the rate of cases that need treatment for threatened premature labor, such as administration of tocolysis agents and antibiotics.

This study did have some limitations. First, we could not examine the effect of cerclage on the patients with infection or inflammation of the lower genital tract because we noted the contraindication of a cerclage for these patients.[21] Second, we had difficulties in obtaining participation agreements for this study from the patients. Surprisingly, an RCT is not especially familiar to most obstetrical patients. In particular, most patients often refuse to accept computer-based allocation. We have to make patients in Japan aware of the importance of RCT. Third, no patient was treated with progesterone in this study; therefore, we did not evaluate the preventive effect of progesterone. This group of pregnant women with cervical length $<$ 25 mm, without infection/vaginal inflammation, and without previous PTB, would benefit from progesterone, as mentioned in the publications that used this drug in patients with similar characteristics.

In conclusion, for women with a short cervical length $<$ 25 mm between 16 and 26 weeks of gestation and singleton pregnancy, mainly without previous PTB, Shirodkar cerclage can be considered. After a full explanation of benefits and risks is provided, we recommend this procedure for patients who prefer surgery rather than bedrest for a long period and those who already have some children, in order to reduce the occurrence of threatened preterm labor.

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Disclosure

None of the authors has any financial interest with any companies.

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