INTRODUCTION

It is widely accepted that conization or loop electrosurgical excision procedure to remove cervical intraepithelial lesions is associated with an increased risk of preterm birth. Although the reason for this increase is unclear, cervical cerclage is widely performed to prevent preterm birth in patients with a previous history of conization. Currently, the practice of prophylactic cerclage is not based on firm evidence. Several retrospective case-control and cohort studies, as well as a systematic review, have indicated that the cerclage procedure may not prevent preterm birth. One retrospective cohort study even reported that the risk of early preterm birth (≤34 weeks of gestation) is increased with cerclage. However, those studies suffered from a small number of subjects. To overcome the limitation of small sample sizes, Cho, et al. used the claims database of the National Health Insurance Service (NHIS) of Korea to look at the risk of preterm birth after conization. In the report, they in-
Study population
We performed a retrospective cohort study of customized health information from the NHIS claims database, which covers about 97% of the entire population of Korea (the remaining 3% are covered by Medical Aid). The NHIS data can be extracted and used for research purposes upon request (https://nhiss.nhis.or.kr). We identified all women who underwent conization procedures between 2002 and 2018 and had a singleton delivery between 2013 and 2018 using diagnoses based on the International Classification of Disease, 10th revision codes (ICD-10) and procedure codes.

As part of the NHIS program, subscribers and beneficiaries who satisfy specific criteria are invited to participate in a bimannual National Health Screening Examination (NHSE), and their screening results are recorded in the NHIS database. The NHSE program includes a health examination and interview, which encompasses questions regarding demographic, socioeconomic, and lifestyle status. We only included subjects who had taken part in the NHSE program within 2 years before their first delivery after cerclage. Women with multiple pregnancies, patients on Medical Aid, and a second or more pregnancies after delivery after cerclage, who have undergone conization. However, the timing of the procedure may matter because if the cerclage was performed when they had symptoms of cervical insufficiency, such as cervical dilatation and bulging membranes, an increased risk of preterm birth may have already been present. Therefore, it would be very informative to evaluate the risk of preterm births according to the timing of the procedure.

The purpose of this study was to determine if the risk of preterm birth is higher in patients with cerclage after conization before pregnancy, compared to patients without cerclage, and to evaluate if there is a difference in the risk of preterm birth according to the timing or indications of cerclage after conization using the NHIS claims database.

Identification of outcomes and baseline characteristics
The primary outcome was frequency of preterm births. The secondary outcomes were frequency of preterm labor and preterm premature rupture of membranes (PROM), length of stay at admission and number of admissions before delivery, antibiotics use, tocolytics use, and the rate of cesarean delivery. Preterm birth was defined as birth before 37 weeks of gestation, and ICD-10 codes O60.1 and O60.3 were used to search the database. For the identification of preterm labor and preterm PROM, the ICD-10 codes O60.x and O42.x were used, respectively.

We collected baseline factors from NHSE data to adjust for possible confounders and included the following variables: age, body mass index (BMI), exercise, alcohol consumption, and smoking. BMI was calculated using height and weight measurements, and it was categorized as low weight (<18.5 kg/m²), normal weight (18.5–22.9 kg/m²), overweight (23.0–24.9 kg/m²), and obese (≥25 kg/m²), which was adopted from cutoffs established for South Korean adults, proposed by the Korean Society for the Study of Obesity.12 Economic status was categorized into four groups: low, low-middle, middle-high, and high. Alcohol consumption was categorized as non-drinker or active drinker: active drinker was defined as drinking alcohol more than four times per week or more than four drinks at a time. Pre-pregnancy smoking was categorized as current (at the time of NHSE health interview) or non-smoker. The exercise was also categorized as non- or active, and active exercise was defined as more than three high-intensity workouts per week or more than five intermediate workouts per week. Residential area was divided into three categories: Capital area (Seoul, Gyeonggi), Metropolitan area (Incheon, Daegu, Gwangju, Busan, Daegu, Ulsan), and Others. Diagnosis of hypertension before pregnancy was based on the relevant ICD-10 code and prescription information. Charlson comorbidity index was calculated as a measure of comorbid disease status. To do so, a weighted score was assigned to each of 17 comorbidities based on 1-year mortality. The sum of the index score is an indicator of disease burden and a strong estimator of mortality. We calculated the index using appropriate ICD-10 codes.13

Differentiation of the type of cerclage
As most prophylactic cerclages are performed at or before 14 weeks of gestation, we categorized cerclages using the timing of maternal serum alpha-fetoprotein (MSAFP) testing, which is usually performed between 15 and 20 weeks of gestation. Cerclages performed at or before the MSAFP test were considered as early cerclages, and those performed after the test were considered as late cerclages. First, the frequencies of pregnancy outcomes were compared between the cerclage and no cerclage groups. Then, outcomes between early cerclage and no cerclage groups were compared.

Statistical analysis
Continuous and categorical variables were compared using Student’s t-test and chi-square test, respectively. Logistic regression analyses were performed to account for possible confounders, such as maternal age, years from conization to delivery, level of income, residential area, Charlson comorbidity index, smoking, drinking, exercise, and BMI. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Statistical analyses
were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). A p value <0.05 was considered significant.

RESULTS

There were 2354129 deliveries from 1893636 women between 2013 and 2018 in Korea and 861047 women who received NHSE within 2 years before delivery. We included 8322 subjects in the analysis after excluding second deliveries after conization, patients with missing values for the variables in the NHSE questionnaires, multiple pregnancies, and Medical Aid recipients among 14050 women who received conization before delivery during this period (Fig. 1).

Table 1 shows the baseline characteristics of the study population. Maternal age, years from conization to delivery, residential area, Charlson comorbidity index, and pregnancy history before the first pregnancy after conization differed between the cerclage and no cerclage groups. Level of income, smoking, drinking, and exercise were not different between the two groups.

We compared the outcomes between cerclage and no cerclage groups (Table 2). The frequency of admissions before delivery was 99.66% in the cerclage group and 19.73% in the no cerclage group. The mean number of admissions was 0.25±0.59 in the no cerclage group and 1.44±0.76 in the cerclage group. Antibiotics and tocolytics use was more frequent in the cerclage group. Preterm birth was significantly more frequent in the cerclage group than in the no cerclage group (8.34% vs. 3.15%, p<0.0001). Cesarean delivery, preterm labor, and preterm PROM were more frequent in the cerclage group than in the no cerclage group, the differences in which were all statistically significant.

We stratified patients according to the timing of surgery using MSAFP testing. After removing the patients without information on the timing of the MSAFP testing, there were 5749 women without cerclage, 669 women with cerclage before the MSAFP measurement, and 291 women with cerclage after the MSAFP measurement. Fig. 2 illustrates the number of patients who underwent cerclage according to the days from MSAFP testing. The histogram shows bimodal characteristics with peak incidence on the day of MSAFP testing.

Table 3 shows the outcomes of the patients according to the timing of cerclages. The number of admissions was higher in both the early cerclage (1.41±0.76) and late cerclage (1.47±0.77) groups than in the no cerclage group (0.26±0.6). The frequency of admission was nearly 100% in both the early and late cerclage groups, compared to only 20.39% in the no cerclage group. The frequency of preterm births was higher even after adjustment for maternal age, years from conization to delivery, level of income, residential area, Charlson comorbidity index, smoking, drinking, exercise, and BMI in both the early (2.77% vs. 8.34% in the cerclage group and 3.15% in the no cerclage group).
Cerclage to Prevent Preterm Birth after Conization

4.48%, \( p=0.0179 \); adjusted OR 2.42, 95% CI 1.49, 3.92) and late cerclage group (2.77% vs. 11%, \( p<0.0001 \); adjusted OR 4.82, 95% CI 3.18, 7.3), compared to the no cerclage group. Antibiotics and tocolytics use, preterm labor, and cesarean delivery also were more frequent in the early cerclage group than in the no cerclage group, and the differences were statistically significant. The risk of preterm PROM was higher in the early cerclage group, with an OR of 1.62 (95% CI 1.31, 2.01), and in the late cerclage group, with an OR of 1.74 (95% CI 1.33, 2.27), compared to the no cerclage group, after adjustment.

**DISCUSSION**

The principal finding of this study is that there is an increased risk of preterm birth in women who undergo a cerclage after conization, compared with no cerclage. Even when the risk of preterm birth was compared between early and no cerclage using the timing of MSAFP testing, the risk of preterm birth was increased. As prophylactic cerclages are usually performed at

**Table 1. Baseline Characteristics of the Study Population**

|                      | No cerclage (n=7147) | Cerclage (n=1175) | \( p \) value |
|----------------------|----------------------|-------------------|--------------|
| Age (yr)             | 33.63±4.03           | 33.90±3.98        | 0.0356       |
| Years from conization to delivery | 4.06±2.81           | 3.69±2.61        | <0.0001      |
| Income level         |                      |                   | 0.1845       |
| Low                  | 1016 (14.22)         | 194 (16.51)       |              |
| Middle-low           | 1924 (26.92)         | 304 (25.87)       |              |
| Middle-high          | 2725 (38.13)         | 448 (38.13)       |              |
| High                 | 1482 (20.74)         | 229 (19.49)       |              |
| Location             |                      |                   | <0.0001      |
| Capital area         | 3922 (54.88)         | 427 (36.34)       |              |
| Metropolitan area    | 1720 (24.07)         | 330 (28.09)       |              |
| Others               | 1505 (21.06)         | 418 (35.57)       |              |
| Charlson Comorbidity Index | <0.0001 |                   |              |
| 0                    | 4312 (60.33)         | 660 (56.17)       |              |
| 1                    | 1956 (27.37)         | 317 (26.98)       |              |
| 2+                   | 879 (12.30)          | 198 (16.85)       |              |
| Pregnancy Hx before the first pregnancy after conization | <0.0001 |                   |              |
| No                   | 5031 (70.39)         | 213 (18.13)       |              |
| Yes                  | 2116 (29.61)         | 962 (81.87)       |              |
| Smoking              |                      |                   | 0.2358       |
| No                   | 6784 (94.92)         | 1105 (94.04)      |              |
| Yes                  | 363 (5.08)           | 70 (5.96)         |              |
| Drinking             |                      |                   | 0.2795       |
| No                   | 5668 (79.31)         | 915 (77.87)       |              |
| Yes                  | 1479 (20.69)         | 260 (22.13)       |              |
| Exercise             |                      |                   | 0.2287       |
| No                   | 4339 (60.71)         | 691 (58.81)       |              |
| Yes                  | 2808 (39.29)         | 484 (41.19)       |              |
| BMI                  |                      |                   | 0.2532       |
| Underweight (<18.5)  | 807 (11.29)          | 123 (10.47)       |              |
| Normal (18.5–22.9)   | 4324 (60.50)         | 693 (58.98)       |              |
| Overweight (23.0–24.9)| 1020 (14.27)         | 171 (14.55)       |              |
| Obese (25.0 or over) | 996 (13.94)          | 188 (16.00)       |              |

Hx, history; BMI, body mass index. Data are presented as a n (%) or mean±standard deviation.

**Table 2. Patient Outcomes in the Cerclage and No Cerclage Groups**

|                      | No cerclage (n=7147) | Cerclage (n=1175) | \( p \) value | Unadjusted OR (95% CI) | Adjusted OR (95% CI)* |
|----------------------|----------------------|-------------------|---------------|------------------------|------------------------|
| No. of admissions    | 0.25±0.59            | 1.44±0.76         | <0.0001       |                        |                        |
| Admissions before delivery | 1410 (19.73)    | 1171 (99.66)      | <0.0001       |                        |                        |
| Antibiotics use      | 230 (3.22)           | 159 (13.53)       | <0.0001       | 4.71 (3.81, 5.82)       | 6.11 (4.73, 7.9)       |
| Tocolytics use       | 316 (4.42)           | 259 (22.04)       | <0.0001       | 6.11 (5.12, 7.3)        | 8.76 (6.93, 11.06)     |
| Cesarean delivery†   | 2901/6594 (43.99)    | 545/1042 (52.3)   | <0.0001       | 1.4 (1.23, 1.59)        | 1.6 (1.38, 1.85)       |
| Preterm labor        | 803 (11.24)          | 419 (35.66)       | <0.0001       | 4.38 (3.81, 5.04)       | 5.97 (5.03, 7.07)      |
| Preterm birth        | 225 (3.15)           | 98 (8.34)         | <0.0001       | 2.8 (2.19, 3.58)        | 4.02 (3.01, 5.37)      |
| Preterm PROM         | 1639 (22.93)         | 307 (26.13)       | 0.0182        | 1.19 (1.03, 1.37)       | 1.72 (1.47, 2.02)      |

OR, odds ratio; CI, confidence interval; PROM, premature rupture of membranes. Data are presented as a n (%) or mean±standard deviation.

*Adjusted for maternal age, years from conization to delivery, level of income, residential area, Charlson comorbidity index, smoking, drinking, exercise, and body mass index. †Hypertension was additionally adjusted. ‡Type of delivery was not identified in 683 deliveries.
Table 3. Patient Outcomes according to the Timing of Cerclages

| Timing of Cerclage | No. of admissions | Antibiotics use | Cesarean delivery | Preterm labor | Preterm birth | Preterm PROM |
|-------------------|------------------|-----------------|-------------------|---------------|--------------|-------------|
| No cerclage (n=5749) | 1.41 (0.10) | 2.67 (4.64) | 2314/5294 (43.71) | 663 (11.53) | 159 (2.77) | 1336/2374 (56.28) |
| Early cerclage (n=669) | 1.41 (0.10) | 2.67 (4.64) | 2314/5294 (43.71) | 663 (11.53) | 159 (2.77) | 1336/2374 (56.28) |
| Late cerclage (n=291) | 1.41 (0.10) | 2.67 (4.64) | 2314/5294 (43.71) | 663 (11.53) | 159 (2.77) | 1336/2374 (56.28) |

Data are presented as a n (%) or mean ± standard deviation.

†Adjusted OR
‡Unadjusted OR
§Admissions before delivery
‖Tocolytics use
¶Mode of delivery was not identified in 558 deliveries.
|||
to consider in interpreting our results. The NHIS data do not provide detailed information on the patients’ condition. Although we used the timing of MSAFP testing to differentiate between types of cerclage, the classification might have been incorrect in some of the patients. It seems that a significant number of late cerclages were included within 1–2 weeks after MSAFP testing. The prophylactic cerclage might have been decided after MSAFP testing. Second, the diagnoses of maternal complications were based on insurance claims data from the NHIS database. As the data were designed for cost claim issues and not for research purposes, there may be some misclassifications in the diagnosis. Third, we used the ICD-10 codes O60.1 and O60.3 to search for cases of preterm birth. As a result, indicated as well as spontaneous preterm, births might have been included in the data. Fourth, physicians may decide to perform cerclage based on cervical length. However, such data could not be obtained from the NHIS claims database. Lastly, data collected from the NHSE questionnaire are limited to pre-pregnancy status. Therefore, the data may not reflect the effects of certain behaviors during pregnancy, such as smoking, exercise, and alcohol consumption.

In conclusion, early cerclage performed before MSAFP testing during pregnancy with a history of conization does not prevent preterm birth, but increases the risk of adverse pregnancy outcomes, including admission before delivery, preterm labor, preterm PROM, antibiotics, and tocolytics use, and cesarean delivery. We suggest that cerclage procedures in women with a previous history of conization should not be performed routinely until supported by sound evidence.

ACKNOWLEDGEMENTS

This work was supported by the National Health Insurance Service, Ilsan Hospital (2019-20-028).

This study used NHIS-NSC data (NHIS-2021-1-716), made by National Health Insurance Service.

AUTHOR CONTRIBUTIONS

Conceptualization: Eui Hyeok Kim, Hyun Soo Park, and Jisun Yoon. Data curation: Eui Hyeok Kim, Sang Ah Lee, and Hyun Soo Park. Formal analysis: Hyun Soo Park and Sang Ah Lee. Funding acquisition: Eui Hyeok Kim and Hee-Sun Kim. Investigation: Hyun Soo Park and Eui Hyeok Kim. Methodology: Eui Hyeok Kim and Jisun Yoon. Project administration: Hyun Soo Park and Hee-Sun Kim. Resources: Hyun Soo Park, Hee-Sun Kim, and Jisun Yoon. Supervision: Eui Hyeok Kim and Jisun Yoon. Validation: Eui Hyeok Kim and Sang Ah Lee. Visualization: Hyun Soo Park. Writing—original draft: Hyun Soo Park and Eui Hyeok Kim. Writing—review & editing: Hyun Soo Park and Eui Hyeok Kim. Approval of final manuscript: all authors.

ORCID iDs

Hyun Soo Park https://orcid.org/0000-0002-7873-3234
Hee-Sun Kim https://orcid.org/0000-0002-7546-749X
Sang Ah Lee https://orcid.org/0000-0001-3415-0141
Jisun Yoon https://orcid.org/0000-0002-1368-3707
Eui Hyeok Kim https://orcid.org/0000-0002-3264-3620

REFERENCES

1. Albrechtsen S, Rasmussen S, Thoresen S, Ergens LM, Iversen OE. Pregnancy outcome in women before and after cervical conisation: population based cohort study. BMJ 2008;337:a1343.
2. Bevis KS, Biggio J R. Cervical conization and the risk of preterm delivery. Am J Obstet Gynecol 2011;205:19-27.
3. Heinonen A, Giessler M, Riska A, Paavonen J, Tapper AM, Jakobsson M. Loop electrosurgical excision procedure and the risk for preterm delivery. Obstet Gynecol 2013;121:1063-8.
4. Jakobsson M, Giessler M, Sainio S, Paavonen J, Tapper AM. Preterm delivery after surgical treatment for cervical intraepithelial neoplasia. Obstet Gynecol 2007;109(2 Pt 1):309-13.
5. Kyrgiou M, Athanasiou A, Kallialla IEJ, Paraskavaidi M, Mitra A, Martin-Hirsch FP, et al. Obstetric outcomes after conservative treatment for cervical intraepithelial lesions and early invasive disease. Cochrane Database Syst Rev 2017;11:CD012847.
6. Sadler L, Safitras A, Wang W, Exeter M, Whittaker J, McCowan L. Treatment for cervical intraepithelial neoplasia and risk of preterm delivery. JAMA 2004;291:2100-6.
7. Nam KH, Kwon JY, Kim YH, Park YW. Pregnancy outcome after cervical conization: risk factors for preterm delivery and the efficacy of prophylactic cerclage. J Gynecol Oncol 2010;21:225-9.
8. Shin MY, Soo ES, Choi SJ, Oh SY, Kim BG, Bae DS, et al. The role of prophylactic cerclage in preventing preterm delivery after electrosurgical conization. J Gynecol Oncol 2010;21:230-6.
9. Grabovac M, Lewis-Mikhael AM, McDonald SD. Interventions to try to prevent preterm birth in women with a history of conization: a systematic review and meta-analyses. J Obstet Gynaecol Can 2019;41:76-88.e7.
10. Rafaeli-Yehudai T, Kessous R, Aricha-Tamir B, Sheiner E, Erez O, Meirovitz M, et al. The effect of cervical cerclage on pregnancy outcomes in women following conization. J Matern Fetal Neonatal Med 2014;27:1594-7.
11. Cho GJ, Ouh YT, Kim LY, Lee TS, Park GU, AHN KH, et al. Cerclage is associated with the increased risk of preterm birth in women who had cervical conization. BMC Pregnancy Childbirth 2018;18:277.
12. Oh SW, Shin SA, Yun YH, Yoo T, Huh BY. Cut-off point of BMI and obesity-related comorbidities and mortality in middle-aged Koreans. Obes Res 2004;12:2031-40.
13. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Martin-Matthews M, et al. The effect of cervical cerclage on pregnancy outcomes in women following conization. J Matern Fetal Neonatal Med 2014;27:1594-7.
14. Berghella V. Cervical insufficiency [accessed on 2021 March 7]. Available at: https://www.uptodate.com/contents/cervical-insufficiency#H263423507.
15. Lazur P, Gueguen S, Dreyfus J, Renaud R, Pontonnier G, Papiernik E. Multicentred controlled trial of cervical cerclage in women at moderate risk of preterm delivery. Br J Obstet Gynaecol 1984;91:731-5.
16. Rush RW, Isaacs S, McPherson K, Jones L, Chalmers I, Grant A. A randomized controlled trial of cervical cerclage in women at high risk of spontaneous preterm delivery. Br J Obstet Gynaecol 1984;91:724-30.
17. MRC/RCOG Working Party on Cervical Cerclage. Macnaughton MC, Chalmers IG, Dubowizt V, Dunn PM, Grant AM, et al. Final report of the Medical Research Council/Royal College of Obstet-

https://doi.org/10.3349/ymj.2021.62.12.1083
tricians and Gynaecologists multicentre randomised trial of cervical cerclage. Br J Obstet Gynaecol 1993;100:516-23.
18. Miyakoshi K, Itakura A, Abe T, Kondoh E, Terao Y, Tabata T, et al. Risk of preterm birth after the excisional surgery for cervical lesions: a propensity-score matching study in Japan, J Matern Fetal Neonatal Med 2021;34:845-51.
19. Zeisler H, Joura EA, Bancher-Todesca D, Hanzal E, Gitsch G. Prophylactic cerclage in pregnancy. Effect in women with a history of conization. J Reprod Med 1997;42:390-2.
20. Berghella V, Odibo AO, To MS, Rust OA, Althuisius SM. Cerclage for short cervix on ultrasonography: meta-analysis of trials using individual patient-level data. Obstet Gynecol 2005;106:181-9.