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Short- and Long-Term Neonatal Outcomes According to Cerclage in Nulliparous Singleton Women: A National Cohort Study Over 15 Years

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ABSTRACT

Background: This study assessed short- and long-term neonatal outcomes in nulliparous women with singleton pregnancies who underwent cerclage compared with those who did not.
Methods: This nationwide retrospective cohort study included all singleton nulliparous women from the Korean National Health Insurance Service database with live births between January 2006 and December 2019. Women were categorized into three groups based on gestational age at cerclage placement: < 16 weeks, 16–24 weeks, and > 24 weeks. We compared short-term neonatal outcomes of preterm birth rates, admission to a neonatal intensive care unit, and composite neonatal morbidity and long-term outcomes (including mortality and developmental problems) of the cerclage groups against those who did not undergo cerclage placement.
Results: A total of 2,896,271 women and their neonates were included in this study, with a median follow-up period of 10.4 years. The cerclage group had a higher rate of preterm birth compared with the control group (control: 2.9%, cerclage at < 16 weeks: 9.8%, 16–24 weeks: 18.2%, > 24 weeks: 36.4%). The cerclage group also showed higher rates of admission to the neonatal intensive care unit and composite neonatal morbidities within 1 month and 1 year compared with the control group. The cerclage group had a significantly higher risk of all-cause mortality compared with the control group (cerclage at < 16 weeks: adjusted hazard ratio [HR], 1.49; 95% confidence interval [CI], 0.88–2.52; at 16–24 weeks: HR, 2.07; 95% CI, 1.29–3.33; at > 24 weeks: HR, 15.85; 95% CI, 11.06–22.71). The rate of developmental problems, including autism, attention-deficit/hyperactivity disorder, cerebral palsy, and developmental delay, was significantly greater in the cerclage group than in the control group. Cerclage placement after 24 weeks was associated with a higher risk of autism (adjusted HR, 2.31; 95% CI, 1.37–3.91), attention-deficit/hyperactivity disorder (HR, 1.70; 95% CI, 1.17–2.45), cerebral palsy (HR, 19.32; 95% CI, 14.63–25.53), and cognitive developmental delay (HR, 1.81; 95% CI, 1.25–2.62) after adjusting for confounders including neonatal birth weight.

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Oh SY. Data curation: Kang D, Hong SY, Cho J. Formal analysis: Park H. Funding acquisition: Oh SY, Sung JH. Investigation: Oh SY, Sung JH. Methodology: Oh SY, Sung JH. Validation: Oh SY, Choi SJ, Roh CR. Writing - original draft: Oh SY, Sung JH, Kang D. Writing - review & editing: Oh SY, Lee YR, Ham S, Cho J, Choi SJ, Roh CR.

Conclusion: Cerclage placement in nulliparous women without a history of miscarriage or stillbirth can be associated with adverse short- and long-term developmental problems in offspring. This study underscores the importance of adhering to evidence-based guidelines when considering cerclage placement.

Keywords: Cervical Cerclage; Short-Term Neonatal Outcomes; Long-Term Neonatal Outcomes; Nulliparous; Singleton

INTRODUCTION

Cervical insufficiency is responsible for 8% of mid-trimester losses,[1] and cerclage is a common obstetric intervention performed globally in cervical insufficiency to salvage fetuses in the periviable period.[2] Current guidelines categorize indications for cerclage as history, ultrasound, or physical examination.[3-5] However, most national guidelines recognize that few randomized clinical trials (RCTs) support the clinical practices of cerclage. Additionally, meta-analyses often include many retrospective studies, which are susceptible to selection bias.

Regarding history-indicated cerclage, two RCTs found no significant improvement in outcomes among women with a history of preterm birth,[6,7] while one found fewer deliveries (13%; 83/647) before 33 weeks of gestation in the cerclage group compared with the non-cerclage group (17%; 110/645, $P = 0.03$).[8] For physical examination–indicated cerclage, only one RCT, which included a small study population (13 women in the cerclage group and 10 women in the bed rest group) has been published and reported prolongation by four weeks of pregnancies with emergent cerclage placement.[9] A meta-analysis on this subject included several retrospective studies with varied selection criteria, leading to inconclusive interpretations.[10] Ultrasound-indicated cerclage, particularly in women with a singleton pregnancy, a short cervical length, and a history of spontaneous second-trimester loss or preterm birth, was studied in four RCTs, all of which reported a significant reduction in birth before 35 weeks of gestation.[11-15]

International guidelines, including those of the American College of Obstetricians and Gynecologists (ACOG), Royal College of Obstetricians and Gynaecologists, Society of Obstetricians and Gynaecologists of Canada, and International Federation of Gynecology and Obstetrics, do not recommend cervical cerclage for women with singleton pregnancies who lack a history of preterm delivery or spontaneous loss.[3-5,16] Despite these guidelines, clinicians sometimes perform cerclages on nulliparous women without such histories, often influenced by maternal concern. Many variations in the clinical management of prevention of preterm birth, including cerclage, have been reported.[17,18] Complications from cerclage are poorly documented and often indistinguishable from risks inherent to the underlying condition.[4] Short- and long-term outcomes of cerclage have never been comprehensively evaluated worldwide.[10] Given that the primary endpoint of all preventive measures should be the long-term health and quality of life of both the mother and child, as suggested by the Core Outcomes in Women's Health initiative,[19] an evaluation of the long-term outcomes of cerclage is imperative.

We hypothesized that it is not common for nulliparous women with singleton pregnancies to require cerclage, in adherence with international guidelines, except in cases where fetal membranes are exposed or bulging. For our study, we excluded women with a history of second-trimester pregnancy loss (due to either abortion or stillbirth) or prior preterm birth

factors that commonly contribute to a diagnosis of cervical insufficiency.[3] Using 15 years of data from the Korean National Health Insurance Service (K-NHIS), we compared short- and long-term neonatal outcomes following cerclage in nulliparous women with singleton pregnancies. We further divided the cerclage group into three subgroups based on gestational age at the time of cerclage placement: < 16, 16–24, and > 24 weeks. The gestational age cutoff of 16 weeks was chosen because the period before this point is rarely complicated by fetal-membrane exposure in singleton pregnancies.[9,20] The gestational age cutoff of 24 weeks was chosen because cerclage placement after 24 weeks is not recommended by most national guidelines due to the potential risk of iatrogenic membrane rupture and subsequent preterm birth.[3,5]

METHODS

Data source and study cohort

We conducted a nationwide retrospective cohort study using the K-NHIS database, which includes data from 99% of the population of Republic of Korea, or approximately 50 million people, from 2005 to 2019.[21] The K-NHIS database is representative of the entire South Korean population and comprises national records of all insured inpatient and outpatient visits, procedures, and prescriptions.

Our cohort included all pregnancies resulting in live births between January 1, 2005, and December 31, 2019. These pregnancies were identified using the procedure codes of delivery (**Supplementary Table 1**). We included all live-born infants who were linked with their mothers. We included nulliparous women (N = 3,685,949) and excluded women with a history of miscarriage (International Statistical Classification of Diseases and Related Health Problems, 10th revision [ICD-10] code: O03, O04 or N96) or stillbirth (ICD-10 code: O36.4 or P95) (n = 745,209). Women with twins in the index pregnancy (n = 66,894) and those who underwent transabdominal cerclage (procedure code R4283) (n = 623) were also excluded. Women hospitalized for more than seven days post-cerclage (n = 8,392) were excluded because they are more likely to possess inevitable risk factors for preterm delivery, such as preterm labor or premature rupture of membranes. Patients were excluded when the sex and age of the mother or infant were missing (n = 67). The final cohort size was 2,896,217.

Measurements

The K-NHIS data contain individual-level demographics along with comprehensive records of diagnosis and healthcare usage, including drug prescriptions and medical procedures across inpatient, outpatient, and emergency department visits. Claims for these services are coded according to the ICD-10.[22]

Women who underwent cerclage were defined by procedure code R4281, R4282, or R4284.

Gestational age was calculated using an algorithm designed to estimate gestational age in administrative databases.[23] Women who had undergone cerclage were assigned to one of the following three groups according to gestational age at the time of the cerclage placement: < 16 weeks, 16–24 weeks, and > 24 weeks.

The primary short-term outcome was composite morbidity, defined as one or more of the followings: transient tachypnea, respiratory distress syndrome, necrotizing enterocolitis, intraventricular haemorrhage, bronchopulmonary dysplasia, and sepsis.

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For long-term outcomes, infants were followed from birth until an event, death, or the end of the study period (December 2020), whichever came first. The primary long-term outcome included one or more of the following prespecified neurological and neurodevelopmental diagnoses: autism spectrum disorder, attention-deficit/hyperactivity syndrome, cerebral palsy, any developmental delay (including motor or cognitive delays), epileptic and febrile seizures, and tics and stereotypic behavior. These clinical outcomes were identified through diagnostic records coded according to the ICD-10 (**Supplementary Table 1**). Given that the K-NHIS routinely audits these claims, its data are considered reliable and have been used in numerous peer-reviewed publications.[24,25] In a validation study comparing our database with electronic medical records, the overall positive predictive value of diagnosis records was 82%.[26]

Various covariates were considered potential confounders or proxies thereof. These included maternal age, as well as maternal comorbidities such as a history of congestive heart failure, diabetes mellitus, renal disease, and cancer within the past year prior to birth and were summarized using the Charlson index.[27,28] Additional factors of hypertension (ICD-10 codes I10-I13 and I15), hypertensive disorder during pregnancy (ICD-10 codes O14, O11, O15, O13, O16, I10, and O10), gestational diabetes mellitus (ICD-10 codes O244 and O249), and overt diabetes (ICD-10 codes O240, O241, O242, O243, E10, E11, E12, E13, and E14) were also included. Birth weight was obtained from infant health screening exams.

Statistical analysis

For the short-term outcome, odds ratio (OR) with 95% confidence interval (CI) were calculated using logistic regression. For long-term outcomes, person-time was measured from the date of birth to the date of event occurrence, death, or the last follow-up, whichever came first. Hazard ratio (HR) with 95% CI values were estimated using Cox proportional hazards regression models and compared with those of the control group. The proportional hazards assumption was assessed using plots of the log (−log) survival function and Schoenfeld residuals. To control confounding factors, we adjusted for maternal age, Charlson index scores, hypertensive disorder during pregnancy, gestational diabetes mellitus, overt diabetes, cesarean delivery, and neonatal sex.

To minimize selection bias, we conducted a sensitivity analysis using a restricted control group. Specifically, we defined the control group as nulliparous singleton pregnant women with a short cervical length but without a history of preterm delivery, as such women are not candidates for cerclage placement. These women were identified based on a prescription for progesterone received after 16 weeks of gestation.

All analyses were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were carried out using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA) and R version 3.3.2 (Free Software Foundation, Inc., Boston, MA, USA).

Ethics statement

The requirement for informed consent was waived by the board, given the study's use of anonymized claims data. The study was approved by the Institutional Review Board of Samsung Medical Center, Republic of Korea (SMC 2021-08-107).

RESULTS

Study population

The mean age of the study population was 32 years. Among all study participants, 7,974 women (0.3%) underwent cerclage with 48.2% undergoing cerclage before 16 weeks (n = 3,845), 40.9% undergoing cerclage at 16–24 weeks (n = 3,262), and 10.9% undergoing cerclage after 24 weeks of gestation (n = 867), respectively. **Table 1** summarizes the baseline characteristics of the study population. Women from the cerclage group were more likely to be older and have more comorbidities compared with the control group. Additionally, the cerclage group was more likely to undergo cesarean delivery, and their infants tended to have lower birth weights compared with those in the control group. The sensitivity analysis found no significant differences in maternal age, Charlson index, or neonatal birth weight between the control and cerclage groups. However, rates of hypertensive disorders during pregnancy, gestational diabetes mellitus, and cesarean delivery were higher in the cerclage group compared with the control group (**Supplementary Table 2**).

Short-term outcomes

Among the study population, 85,152 (2.9%) experienced preterm delivery. The proportion of women who had preterm deliveries was higher among those who received cerclage (control: 2.9%, cerclage < 16 weeks: 9.8%; 16–24 weeks: 18.2%; > 24 weeks: 36.4%) (**Fig. 1**). The rate of most adverse neonatal outcomes increased incrementally with advanced gestational age at the time of cerclage placement. For example, the proportions of women whose infants developed respiratory distress syndrome within 1 year was ranging from 0.8 % to 16.3% (control: 0.8%; cerclage at > 16 weeks: 1.3%; 16–24 weeks: 4.9%, > 24 weeks: 16.3%) (**Fig. 1**).

Table 2 presents the ORs for short-term neonatal outcomes among women with and without cerclage. Compared with the control group, the adjusted OR for preterm birth was 3.16 (95% CI, 2.83–3.54) for cerclage before 16 weeks, 6.12 (95% CI, 5.57–6.72) for cerclage at 16–24 weeks, and 17.92 (95% CI, 15.52–20.69) for cerclage after 24 weeks of gestation, respectively.

Table 1. Baseline characteristics of the study population

Characteristics	Control (n = 2,888,243)	Cerclage at < 16 wk (n = 3,845)	Cerclage at 16 and 24 wk (n = 3,262)	Cerclage at > 24 wk (n = 867)	*P* value[a]
Maternal					
Maternal age, yr	31.7 ± 4.3	33.9 ± 4.0	33.9 ± 4.4	33.3 ± 4.6	< 0.001
Charlson index	0.4 ± 0.8	0.7 ± 1.0	0.7 ± 1.0	0.7 ± 0.1	< 0.001
History of congestive heart failure	4,265 (0.1)	9 (0.2)	9 (0.3)	2 (0.2)	0.113
History of diabetes mellitus	67,584 (2.3)	202 (5.3)	182 (5.6)	47 (5.4)	< 0.001
History of renal disease	3,415 (0.1)	5 (0.1)	18 (0.6)	4 (0.5)	< 0.001
History of cancer	27,614 (1.0)	189 (4.9)	127 (3.9)	20 (2.3)	< 0.001
History of hypertension	25,501 (0.9)	58 (1.5)	62 (1.9)	26 (3.0)	< 0.001
Hypertensive disorder during pregnancy	711,644 (24.6)	1,267 (33.0)	1,160 (35.6)	329 (37.9)	< 0.001
Diabetes					
Gestational diabetes	647,857 (22.4)	1,149 (29.9)	1,010 (31.0)	284 (32.8)	< 0.001
Overt diabetes	26,536 (0.9)	74 (1.9)	81 (2.5)	23 (2.7)	< 0.001
Caesarean delivery	1,139,401 (39.4)	1,866 (48.5)	1,820 (55.8)	452 (52.1)	< 0.001
Neonatal					
Sex, male	1,496,060 (51.8)	1,797 (46.7)	1,480 (45.4)	362 (41.8)	< 0.001
Birth weight, kg (n = 2,557,294)	3.2 ± 0.5	3.1 ± 0.5	2.8 ± 0.6	2.5 ± 0.9	< 0.001

Values are presented as mean ± standard deviation or number (%).
[a]Linear-by-linear association test was used.

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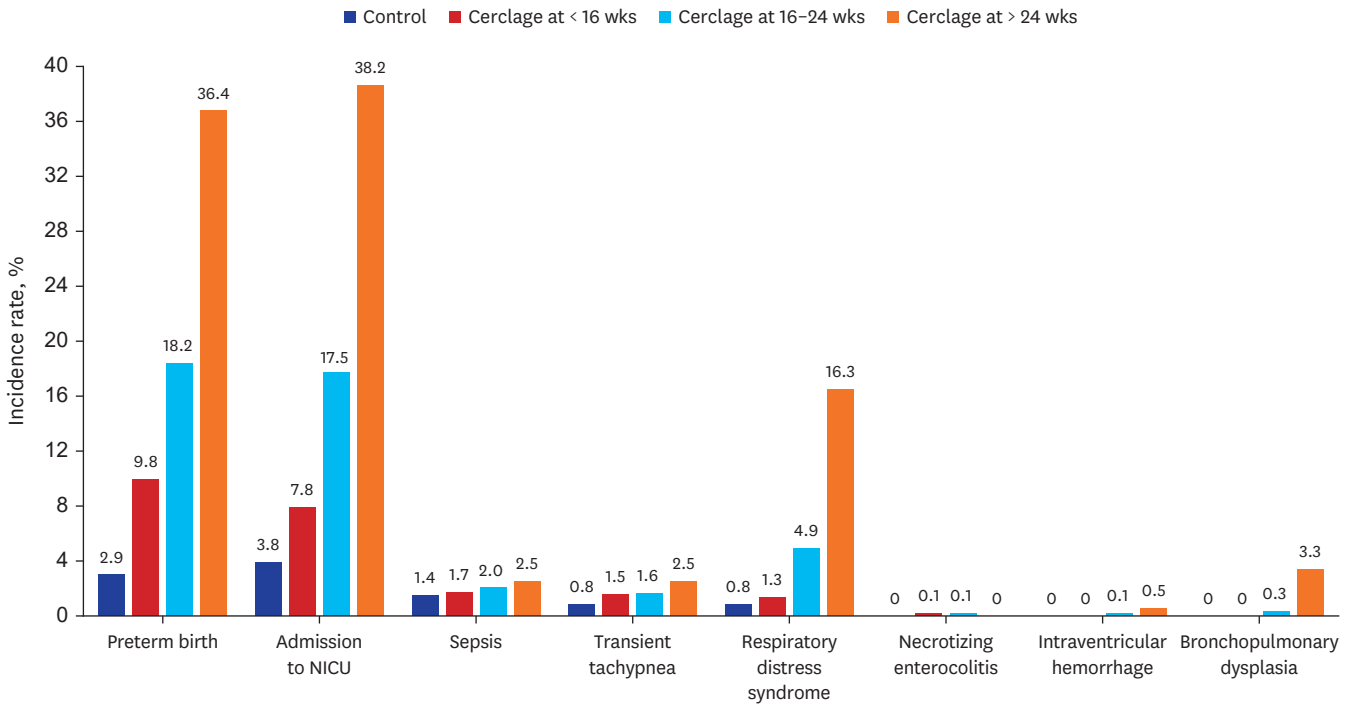

Fig. 1. The prevalence of adverse short-term outcomes in infants within 1 year after birth according to the cerclage placement.
NICU = neonatal intensive care unit.

Table 2. Adjusted OR for short-term outcomes of infants born to women with and without cerclage

Short-term outcome	Control	Cerclage at < 16 wk	Cerclage at 16–24 wk	Cerclage at > 24 wk
Preterm birth	Reference	**3.16 (2.83–3.54)**	**6.12 (5.57–6.72)**	**17.92 (15.52–20.69)**
Outcome within 1 mon				
Neonate intensive care unit	Reference	**1.81 (1.61–2.05)**	**4.27 (3.89–4.69)**	**13.11 (11.36–15.31)**
Composite outcome	Reference	**1.59 (1.34–1.88)**	**2.27 (1.97–2.62)**	**4.10 (3.29–5.10)**
Sepsis	Reference	**1.55 (1.04–2.02)**	**1.52 (1.16–2.05)**	0.70 (0.32–1.57)
Transient tachypnea	Reference	**1.34 (1.02–1.77)**	**1.49 (1.14–1.97)**	**2.23 (1.43–3.47)**
Respiratory distress syndrome	Reference	1.26 (0.91–1.73)	**3.66 (3.00–4.48)**	**8.89 (6.78–11.65)**
Necrotizing enterocolitis	Reference	3.45 (0.86–13.86)	**5.66 (1.81–17.68)**	-
Intraventricular haemorrhage	Reference	-	3.18 (0.45–22.75)	**11.62 (1.62–83.28)**
Bronchopulmonary dysplasia	Reference	-	**7.89 (1.93–32.13)**	**87.71 (34.90–220.45)**
Outcomes during 1 yr				
Neonate intensive care unit	Reference	**1.79 (1.59–2.02)**	**4.30 (3.91–4.72)**	**14.02 (12.16–16.16)**
Composite outcome	Reference	**1.35 (1.18–1.55)**	**2.37 (2.11–2.66)**	**6.24 (5.30–7.34)**
Sepsis	Reference	**1.33 (1.10–1.59)**	**1.46 (1.21–1.77)**	1.29 (0.87–1.91)
Transient tachypnea	Reference	**1.41 (1.08–1.84)**	**1.48 (1.13–1.94)**	**2.39 (1.56–3.66)**
Respiratory distress syndrome	Reference	**1.33 (1.01–1.75)**	**4.61 (3.91–5.43)**	**19.93 (16.51–24.05)**
Necrotizing enterocolitis	Reference	**3.60 (1.16–11.21)**	**5.12 (1.91–13.71)**	-
Intraventricular haemorrhage	Reference	0.96 (0.14–6.82)	3.06 (0.98–9.52)	**16.09 (5.98–43.29)**
Bronchopulmonary dysplasia	Reference	-	**4.25 (2.33–7.74)**	**52.93 (35.82–78.21)**

Data were presented as adjusted OR and 95% confidence interval. Boldwords are presented as an indication of statistical significance.
Adjusted for maternal age, Charlson index, hypertensive disorder during pregnancy, gestational diabetes, overt diabetes, Cesarean delivery, and neonatal sex.
OR = odds ratio.

Additionally, the rates of morbidities within 1 month and within 1 year were both higher in the cerclage group compared with the control group. For example, the adjusted OR for the risk of composite outcomes within 1 month was 1.59 (95% CI, 1.34–1.88) for cerclage before 16 weeks, 2.27 (95% CI, 1.97–2.62) for cerclage between 16 and 24 weeks, and 4.10 (95% CI, 3.29–5.10) for cerclage after 24 weeks of gestation (**Table 2**). Rates of composite outcomes

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within 1 year were also higher in the cerclage group: for cerclage at < 16 weeks, the OR was 1.35 (95% CI, 1.18–1.55), for that at 16–24 weeks, it was 2.37 (95% CI, 2.11–2.66), and, for that after 24 weeks of gestation, it was 6.24 (95% CI, 5.30–7.34), respectively, compared with the control group (**Table 2**). Infants in the group who experienced cerclage after 24 weeks of gestation were more likely to experience respiratory distress syndrome (OR, 19.93; 95% CI, 16.51–24.05) and bronchopulmonary dysplasia (OR, 52.93; 95% CI, 35.82–78.21) within 1 year compared with those in the control group (**Table 2**). Sensitivity analysis indicated that members of the group with cerclage after 24 weeks were four times more likely to experience a composite outcome within both 1 month and 1 year compared with the control group (**Supplementary Table 3**).

Long-term outcomes

During the follow-up period (median, 10.4 years; interquartile range, 6.5–13.7 years), 7,044 infants died. The cerclage group exhibited a significantly higher risk of all-cause mortality compared with the control group (control: 0.24, cerclage at < 16 weeks: 0.37, 16–24 weeks: 0.58, and > 24 weeks: 5.17 per 1,000 person-years) (**Fig. 2**). Compared with the control group, the adjusted HRs for all-cause mortality in the cerclage groups were 1.49 (95% CI, 0.88–2.52) for cerclage before 16 weeks, 2.07 (95% CI, 1.29–3.33) for that 16 - 24 weeks, and 15.85 (95% CI, 11.06–22.71) after 24 weeks of gestation (**Table 3**). Sensitivity analysis revealed that cerclage after 24 weeks of gestation had a higher risk of mortality (HR, 9.60; 95% CI, 4.36–21.14) compared with the control group (**Supplementary Table 4**).

Regarding developmental problems, the incidence rates of autism (16–24 weeks: HR, 1.49; 95% CI, 1.09–2.03; > 24 weeks: HR, 2.31; 95% CI, 1.37–3.91), attention-deficit/hyperactivity disorder (16–24 weeks: HR, 1.36; 95% CI, 1.13–1.63; > 24 weeks: HR, 1.70; 95% CI, 1.17–2.45),

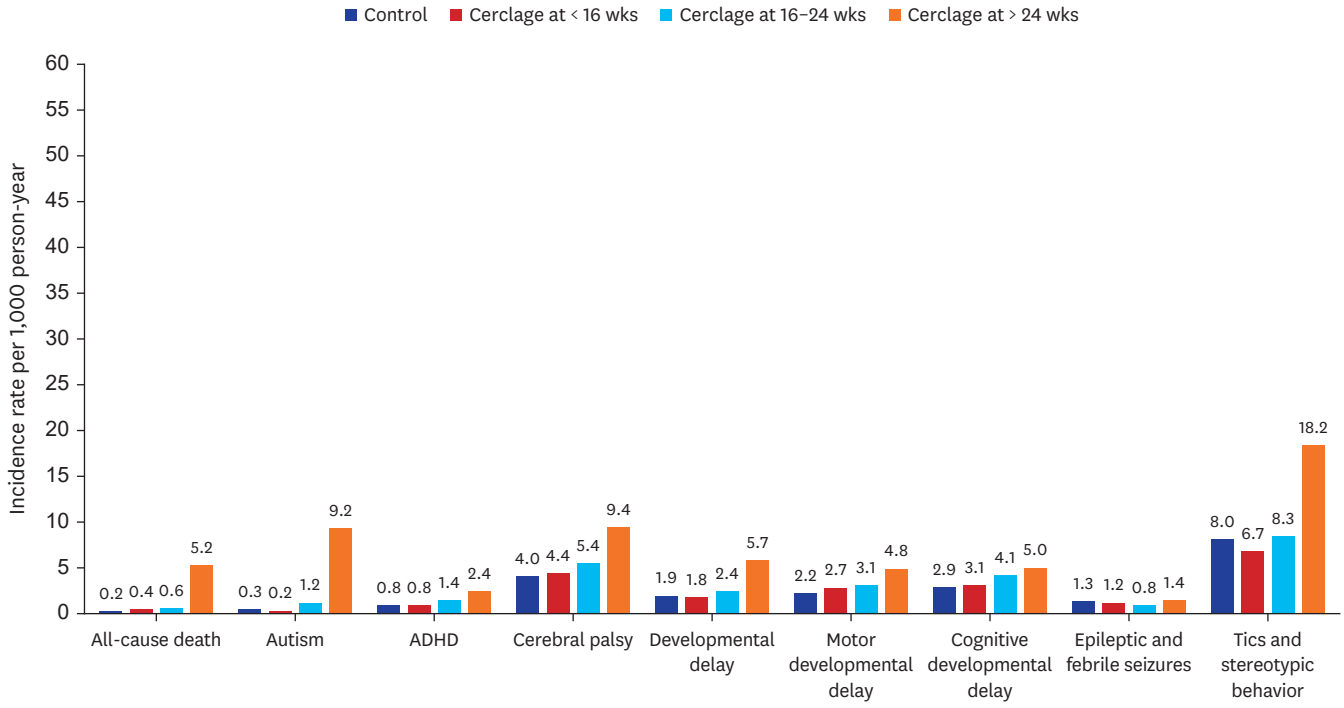

Fig. 2. The prevalence of adverse long-term outcomes of infants according to the cerclage placement.
ADHD = attention-deficit/hyperactivity disorder.

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Table 3. Adjusted HR for long-term outcomes of infants in women with and without cerclage

Long-term outcome	Control	Cerclage at < 16 wk	Cerclage at 16–24 wk	Cerclage at > 24 wk
All-cause death	Reference	**1.49 (0.88–2.52)**	**2.07 (1.29–3.33)**	**15.85 (11.06–22.71)**
Development problem				
Autism	Reference	0.93 (0.65–1.33)	**1.49 (1.09–2.03)**	**2.31 (1.37–3.91)**
ADHD	Reference	1.05 (0.87–1.26)	**1.36 (1.13–1.63)**	**1.70 (1.17–2.45)**
Cerebral palsy	Reference	0.62 (0.31–1.25)	**2.99 (2.13–4.19)**	**19.32 (14.63–25.53)**
Developmental delay	Reference	1.06 (0.91–1.25)	**1.23 (1.05–1.45)**	**1.92 (1.47–2.52)**
Motor developmental delay	Reference	0.91 (0.71–1.16)	1.18 (0.93–1.29)	2.55 (1.82–3.56)
Cognitive developmental delay	Reference	1.19 (0.98–1.45)	**1.29 (1.05–1.59)**	**1.81 (1.25–2.62)**
Epileptic and febrile seizures	Reference	0.85 (0.75–0.97)	1.00 (0.88–1.13)	1.70 (1.39–2.08)
Tics and stereotypic behaviour	Reference	0.88 (0.66–1.19)	0.59 (0.39–0.88)	1.02 (0.51–2.05)

Data are presented as adjusted HR and 95% confidence interval. Bold words are presented as an indication of statistical significance.
Adjusted for maternal age, Caesarean delivery, hypertensive disorder during pregnancy, gestational diabetes, overt diabetes, Charlson's index, neonatal sex, and birth weight.
HR = hazard ratio, ADHD = attention-deficit/hyperactivity disorder.

cerebral palsy (16–24 weeks: HR, 2.99; 95% CI, 2.13–4.19; > 24 weeks: HR, 19.32; 95% CI, 14.63–25.53), and developmental delay (16–24 weeks: HR, 1.23; 95% CI, 1.05–1.45; > 24 weeks: HR, 1.92; 95% CI, 1.47–2.52) were statistically significantly higher in the cerclage group compared with the control group (**Table 3**). Sensitivity analysis indicated that members of the group with cerclage after 24 weeks were more likely to experience cerebral palsy (HR, 4.48; 95% CI, 2.64–7.59), developmental delay (HR, 2.00; 95% CI, 1.38–2.91), and epileptic and febrile seizures (HR, 1.54; 95% CI, 1.18–2.03) compared with the control group (**Supplementary Table 4**).

DISCUSSION

The largest subgroup in our study comprised women who underwent cerclage before 16 weeks of gestation (48.2%). Before excluding women with twin pregnancies, who received transabdominal cerclage or who were hospitalized for more than seven days post-cerclage, the number of cerclage performed in nulliparous women without a history of miscarriage or stillbirth was 12,928 over the study period (2005–2019) in total (n = 4,697 for cerclage at < 16 weeks, n = 5,218 for cerclage at 16–24 weeks, and 3,013 for cerclage at > 24 weeks of gestation). After excluding those women mentioned above (n = 75,049), the proportion of patients who received cerclage after 24 weeks of gestation among study population showed a marked reduction (from 23.81% to 10.87%). This relative reduction contributed to an increase in the proportion of cases before 16 weeks (from 36.33% to 48.22%).

Because we selected only nulliparous women who were not potential candidates for history-indicated or ultrasound-indicated cerclage, by definition, the only plausible reason for cerclage placement in these women would be physical examination–indicated cerclage. However, considering that exposure to fetal membranes in singleton pregnancies usually occurs after 16 weeks,[9,20,29,30] these women are unlikely be the ideal candidates for cerclage, according to most national guidelines,[31] particularly because they lack a history of second-trimester pregnancy loss, either through miscarriage or stillbirth, or a history of preterm delivery. In fact, a meta-analysis already demonstrated that cerclage placement for a short cervical length < 2.5 cm in women without a history of preterm delivery does not improve the rate of preterm delivery before 35 weeks of gestation or neonatal outcomes.[32] Our data reinforce this point, indicating that cerclage placement before 16 weeks was associated with three-fold higher preterm birth rate and a 1.5-fold higher neonatal mortality rate, even after

adjusting for birth weight. These findings underscore the importance of evidence-based, prudent decisions when considering cerclage placement.[33]

Based on our findings, nulliparous women who underwent cerclage at 16–24 weeks experienced a rate of preterm delivery that was approximately six-fold higher than that of the control group. Additionally, the neonatal mortality rate was twice as high, even after adjusting for birth weight. As win the group of women who had cerclage before 16 weeks of gestation, we assumed that cerclage in this group was performed based on a physical examination. As such, a higher rate of adverse outcomes compared with the no-cerclage group was expected and likely reflects a greater risk for subsequent preterm delivery in these women, regardless of cerclage placement. Moreover, these findings align with a recent meta-analysis indicating that perioperative complications of cerclage in singleton pregnancies are highest when cerclage is performed based on a physical examination, compared with ultrasound- or history-indicated cases.[34]

According to the current guidelines, cerclage placement after 24 weeks of gestation is not recommended.[35] For example, the ACOG guidelines note that cerclage should be limited to second-trimester pregnancies before fetal viability is established. Our study found that the group receiving cerclage after 24 weeks of gestation had the poorest short-term and long-term outcomes, including an 18-fold higher rate of preterm delivery and 16-fold higher rate of neonatal mortality. Furthermore, we observed a significant increase in long-term developmental problems, such as autism and cerebral palsy, in such infants, even after adjusting for neonatal birth weight and other confounding factors. One plausible explanation for these results is that cerclage in these nulliparous women was performed under conditions in which the fetal membranes were exposed. Given the elevated rate of microbial invasion or inflammation of the amniotic cavity (50–80%) associated with cervical insufficiency,[36-38] it is likely that women in this group had a substantial degree of intra-amniotic infection or inflammation. This could negatively affect both short-term and long-term outcomes for the infants, as previously documented.[39-41] These findings discourage cerclage in nulliparous singleton women (with no history of abortion or preterm delivery) after 24 weeks of gestation, as recommended by most professional guidelines.[3,16] In this context, the ACOG recommendation that women be counselled about the potential for associated maternal and perinatal morbidity before undergoing a physical examination–indicated cerclage is pertinent.[5]

There is a concern that our results could be misinterpreted to suggest that performing cerclage before 16 weeks is better than performing it after 16 weeks. Comparing cerclage placements before and after 16 weeks does not indicate that earlier placement leads to better outcomes. In fact, when compared to women who did not receive cerclage, outcomes were generally poorer for all cerclage groups, regardless of gestational age at placement. This suggests that performing cerclage in women unlikely to benefit from it is associated with worse outcomes, particularly it is when performed after 24 weeks.

Complications arising from cerclage are not well documented and are often difficult to distinguish from risks inherent to the underlying condition.[4] Possible complications include preterm labor, preterm premature rupture of membranes (PPROM), and infection of fetal membranes. Intraoperative complications such as bladder damage, cervical trauma, membrane rupture, and bleeding are seldom reported (< 1%).[34] A systematic review and meta-analysis indicates that the rates of intraoperative membrane rupture and cervical laceration were 4.1% and 7.9%, respectively, among those undergoing physical

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examination–indicated cerclage.[42] Although history-indicated cerclage is likely to have a lower complication rate compared with physical examination–indicated cerclage, a recent population-based cohort study from Australia showed that even history-indicated cerclage can be associated with worse pregnancy outcomes, including a higher rates of preterm birth, PPROM, stillbirth, and neonatal death as well as severe morbidity in women with a single previous mid-trimester delivery compared with those without cerclage.[43] Based on the national data, the authors suggested caution regarding the potential sequelae of history-indicated cerclage. The ACOG also noted that unnecessary history-indicated cerclage procedures can be avoided by serial transvaginal ultrasonography in more than half of patients.[5,44-46]

Recently, we observed a higher rate of early-onset neonatal sepsis and severe placental inflammation associated with cerclage performed non-adherent to professional guidelines.[47]

Long-term outcomes of obstetric interventions or treatments are relatively under-reported and sometimes associated with a poor subsequent prognosis. For example, antibiotic treatment consisting of erythromycin or co-amoxiclav for preterm labor was unexpectedly associated with an increased risk of cerebral palsy in offspring,[48] resulting in its non-use in contemporary practice. In another example, after *in utero* exposure to beta-mimetics for threatened preterm labor was found to be associated with a higher risk of behavioral disorders like autism in offspring,[5] it was removed from National Institute for Health and Care Excellence guidelines (https://www.nice.org.uk/guidance/ng25). Meanwhile, cerclage and progesterone therapy are the two most frequently introduced obstetric interventions in women with short cervical lengths. Regarding progesterone treatment, several studies have reviewed the long-term effects, and neither benefits nor harms are related to post-neonatal outcomes with antenatal progesterone treatment.[49-52] To our knowledge, no studies have assessed the long-term outcomes in neonates whose mothers underwent cerclage during pregnancy. In our sensitivity analysis, higher rates of mortality and developmental problems were seen in offspring whose mothers underwent cerclage after 24 weeks, even after adjusting for neonatal birth weight, compared with those in mothers treated with progesterone. Collectively, our data indirectly suggest that progesterone is a preferable first-line treatment when these two options are clinically equivalent. We also strongly support the recommendation of vaginal progesterone for cervical length > 2.0 cm in singleton pregnancies without prior preterm birth.[53]

The main limitation of this study is that the national database we used does not include information about cervical length at the time of cerclage, a factor that could influence clinical decision-making in women even without a history of preterm birth or abortion, similar to another population-based study.[54] Second, although we excluded women with prior abortion or delivery, our study population may have included patients with non-obstetric risk factors, such as a history of cervical surgery or intrinsic uterine anomalies. However, the overall frequency of cervical insufficiency, even in these groups, is relatively low, and routine cerclage is not recommended in such women by most national guidelines.[31] As such, these non-obstetric risk factors are unlikely to affect our study's primary findings.

The main strength of this study lies in its large, national population-based cohort, encompassing 2,896,217 women over a 15 year-period. To the best of our knowledge, this is the first study to assess the long-term cumulative outcomes of children whose mothers underwent cerclage.

Cerclage placement in nulliparous singleton women without a history of abortion or stillbirth was associated with higher rates of preterm birth, and infant mortality, and worse long-term developmental problems, including cerebral palsy. We strongly recommend that the decision to perform a cerclage be based on evidence and prudence.[33]

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Hospital codes of study outcomes

Supplementary Table 2

Baseline characteristics of study participants based on the progesterone group as a reference

Supplementary Table 3

Adjusted OR for short-term outcomes of infants in women with and without cerclage based on the progesterone group as a reference

Supplementary Table 4

Adjusted HR for long-term outcomes of infants in women with and without cerclage based on the progesterone group as a reference

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