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Prolonged Indomethacin Therapy Following Cervical Cerclage Is Not Associated With Improved Pregnancy Latency: A Retrospective Cohort Study

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Abstract

Background: Cervical cerclage is an established intervention for the prevention of spontaneous preterm birth (sPTB) in selected high-risk pregnancies. Indomethacin is frequently administered perioperatively because of its anti-inflammatory and tocolytic properties; however, evidence regarding the benefit of prolonged administration following cerclage placement remains limited.

Objective: To evaluate the association between prolonged indomethacin therapy following cervical cerclage and pregnancy latency, spontaneous preterm birth, and maternal outcomes.

Methods: This retrospective cohort study included women who underwent transvaginal cervical cerclage at a tertiary referral center between 2018 and 2022. All patients received perioperative indomethacin therapy and were categorized according to treatment duration as standard-duration (≤48 hours) or prolonged-duration (>48 hours) therapy. The primary outcome was latency from cerclage placement to delivery. Secondary outcomes included spontaneous preterm birth before 34 and 28 weeks of gestation, gestational age at delivery, and clinical chorioamnionitis. Kaplan–Meier survival analysis and multivariable Cox proportional hazards regression were performed to evaluate factors associated with pregnancy latency.

Results: A total of 131 women were included, of whom 54 received prolonged indomethacin therapy and 77 received standard-duration treatment. Baseline maternal characteristics, previous preterm birth history, gestational age at cerclage placement, cervical findings at presentation, and rates of clinical chorioamnionitis were comparable between groups. Women receiving prolonged indomethacin delivered at a lower gestational age than those receiving standard-duration therapy (median 34.0 vs. 37.0 weeks, p=0.009) and experienced higher rates of spontaneous preterm birth before 37 weeks (57.4% vs. 36.4%, p=0.017). Kaplan–Meier analysis demonstrated a significantly shorter latency period in the prolonged-treatment group (median 94.0 vs. 123.0 days; log-rank p<0.001). The rate of spontaneous preterm birth before 34 weeks was not significantly different between groups (27.8% vs. 18.2%, p=0.193). In multivariable Cox regression analysis, prolonged indomethacin administration remained independently associated with an increased hazard of earlier delivery (adjusted hazard ratio 1.728, 95% CI 1.116–2.677, p=0.014).

Conclusions: Prolonged indomethacin administration following cervical cerclage was not associated with improved pregnancy prolongation and was independently associated with a shorter latency period from cerclage placement to delivery. These findings do not support the routine extension of indomethacin therapy beyond the immediate perioperative period after cervical cerclage. Prospective studies are needed to clarify the role of prolonged indomethacin treatment in this population.

Keywords: Cervical cerclage; indomethacin; pregnancy latency; spontaneous preterm birth; cervical insufficiency; short cervix; retrospective cohort

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Introduction

Preterm birth (PTB) remains the leading cause of perinatal morbidity and mortality worldwide and continues to represent a major public health challenge despite advances in obstetric care [1,2]. Approximately 85% of deliveries before 37 weeks of gestation and 90% of deliveries before 34 weeks occur in women without a previous history of PTB [3]. The etiology of PTB is complex and multifactorial, involving maternal, fetal, placental, and cervical factors. Among these, cervical insufficiency (CI) is a well-recognized contributor, affecting approximately 0.5–1.0% of pregnancies [3].

Cervical insufficiency is characterized by painless cervical shortening and dilatation leading to recurrent second-trimester pregnancy loss or spontaneous preterm birth in the absence of uterine contractions [4]. It is estimated to account for approximately 15% of pregnancy losses occurring between 16 and 26 weeks of gestation and represents an important cause of extreme prematurity [4]. Given that nearly half of surviving infants born before 25 weeks experience at least one long-term disability, effective preventive strategies for women at risk of cervical insufficiency are of substantial clinical importance [2,4].

Among the available preventive interventions, cervical cerclage remains the cornerstone of management in carefully selected high-risk pregnancies. Current guidelines recommend cerclage for women with a singleton pregnancy, a history of spontaneous preterm birth, and a short cervix identified by transvaginal ultrasonography [3,4]. Cerclage may also be beneficial in selected women with progressive cervical shortening or advanced cervical changes detected during pregnancy. In particular, examination-indicated (emergency) cerclage is frequently performed in women presenting before fetal viability with painless cervical dilatation and exposed or prolapsed fetal membranes in the absence of labor [2-4]. Without intervention, these patients are at exceptionally high risk of pregnancy loss and extreme preterm birth [5].

Although cervical cerclage has been shown to prolong pregnancy and improve neonatal outcomes, treatment success remains variable [7,8]. Reported pregnancy prolongation following emergency cerclage ranges from approximately 4 to 7 weeks, and substantial heterogeneity exists among studies [8]. This variability suggests that factors beyond mechanical cervical support contribute to treatment outcomes.

Increasing evidence indicates that inflammation plays a central role in the pathogenesis of cervical remodeling, membrane weakening, and spontaneous preterm birth. Subclinical intra-amniotic infection and inflammatory activation have been implicated in both cervical insufficiency and cerclage failure. Furthermore, transvaginal cerclage placement itself may induce a transient inflammatory response associated with increased prostaglandin production. Because prostaglandins are key mediators of uterine activity and cervical ripening, strategies aimed at reducing procedure-related inflammation may improve the effectiveness of cerclage.

Indomethacin, a potent nonsteroidal anti-inflammatory drug and prostaglandin synthesis inhibitor, is commonly administered perioperatively during cervical cerclage placement [9,10]. While short-term perioperative use is widely practiced, the potential benefits of prolonged indomethacin administration following cerclage remain poorly defined. Given the important role of inflammatory pathways in spontaneous preterm birth, extended indomethacin therapy may theoretically enhance cerclage efficacy by suppressing ongoing inflammatory and prostaglandin-mediated processes .

Therefore, the aim of this study was to evaluate whether prolonged indomethacin administration following cervical cerclage is associated with increased latency from cerclage placement to delivery and reduced rates of spontaneous preterm birth.

Methods

This retrospective cohort study included women who underwent transvaginal cervical cerclage at a tertiary referral center between January 2018 and December 2022. Women were excluded if information regarding the cerclage procedure

(indication or suture material) or pregnancy outcomes was unavailable. All medical records were manually reviewed for eligibility. Baseline demographic characteristics, obstetric history, pregnancy course, cerclage-related data, delivery outcomes, and neonatal outcomes were extracted from the electronic medical records. Ethical approval was obtained from the Bursa Uludağ University Faculty of Medicine Clinical Research Ethics Committee (approval number: 2026/329/13-26).

Cerclage indications were classified according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines as history-indicated, ultrasound-indicated, or examination-indicated cerclage [2]. History-indicated cerclage was defined as placement in women with one or more previous mid-trimester pregnancy losses or spontaneous preterm births before 28 weeks of gestation. Ultrasound-indicated cerclage was defined as placement in women with a history of spontaneous preterm birth and a transvaginal cervical length <25 mm. Examination-indicated cerclage was defined as placement in women with asymptomatic cervical dilatation of at least 1 cm detected on digital examination.

In accordance with institutional surveillance protocols, transvaginal cervical length assessment was routinely performed between 18 and 25 weeks of gestation in women considered at increased risk for spontaneous preterm birth. Cerclage was considered in asymptomatic women with a singleton pregnancy, a history of spontaneous preterm birth and/or second-trimester pregnancy loss attributed to cervical insufficiency, and a cervical length <15 mm during the second trimester.

Before cerclage placement, all patients underwent comprehensive clinical evaluation, including physical examination, transvaginal ultrasonography performed by experienced obstetricians or certified sonographers, complete blood count, and measurement of C-reactive protein levels. Patients were carefully assessed for uterine contractions, rupture of membranes, and clinical signs of intra-amniotic infection.

All procedures were performed under spinal anesthesia using the McDonald technique by one of three experienced obstetricians. Non-absorbable polyester braided sutures (Ethibond®) or 5-mm braided polyester tape (Mersilene® tape) were used according to surgeon preference. Patients were placed in the Trendelenburg position, and prolapsed fetal membranes, when present, were gently reduced into the uterine cavity using a Foley catheter inflated with 4–8 mL of saline. The anterior and posterior cervical lips were grasped with atraumatic forceps. A curved needle loaded with a non-absorbable suture was inserted at the cervicovaginal junction, and a purse-string suture was placed circumferentially around the cervix as high as technically feasible while avoiding injury to adjacent structures, including the bladder, rectum, and uterine vessels. Four to six deep bites were taken into the cervical stroma without entering the endocervical canal. The suture was then tied securely, leaving sufficient length to facilitate later removal.

Perioperative prophylaxis consisted of cefazolin (1–2 g) and indomethacin (100 mg) administered before surgery. Following cerclage placement, vaginal progesterone (200 mg daily) was prescribed until 37 weeks of gestation. The duration of progesterone and indomethacin treatment was determined by the managing physician and recorded for subsequent analysis. Although all patients received indomethacin during the first 48 hours following cerclage placement, treatment was prolonged in selected cases at the discretion of the operating surgeon.

Collected variables included maternal demographic characteristics, obstetric history, cervical length measurements, cervical examination findings, cerclage indication, perioperative interventions (antibiotics, indomethacin, and progesterone), pregnancy course, and maternal and neonatal outcomes.

The primary outcome was latency from cerclage placement to delivery, measured in weeks. Secondary outcomes included spontaneous preterm birth (sPTB) before 34 weeks of gestation, spontaneous preterm birth before 28 weeks of gestation, and the rates of clinical and chorioamnionitis.

Spontaneous preterm birth was defined as delivery between 20+0 and 36+6 weeks of gestation resulting from either spontaneous preterm labor or preterm prelabor rupture of membranes. Clinical chorioamnionitis was identified from delivery hospitalization records documenting chorioamnionitis or intra-amniotic infection/inflammation. Histologic chorioamnionitis was determined through review of placental

pathology reports and was considered present when acute or chronic chorioamnionitis was reported.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 26.0; IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables were found to be non-normally distributed; therefore, they were expressed as median with minimum–maximum values. Categorical variables were presented as frequencies and percentages. For univariate comparisons of continuous clinical characteristics and gestational duration outcomes (measured in days) between the two treatment groups (No long-term indomethacin vs. Long-term indomethacin), the non-parametric independent-samples Mann–Whitney U test was utilized. Proportions of categorical outcomes, including the incidence of spontaneous preterm birth before 34 weeks of gestation, were evaluated using the Pearson Chi-square test. For contingency tables with dimensions greater than 2x2 or with expected cell counts less than 5, Fisher's exact test or the Fisher–Freeman–Halton exact test was applied, where appropriate. The strength of categorical associations and effect sizes was quantified using the Phi coefficient for 2x2 tables and Cramer's V coefficient for larger contingency matrices. To model the time-to-delivery interval (pregnancy latency) from the day of cervical cerclage placement to final delivery, survival analysis was conducted via the Kaplan-Meier method, and cumulative survival curves were compared using the log-rank test.

To determine the independent effect of long-term indomethacin administration on pregnancy latency while rigorously controlling for baseline clinical confounders, a multivariable Cox proportional hazards regression model was constructed. The model simultaneously adjusted for potential confounders, including cerclage indication, prior mid-trimester loss/preterm birth history (stratified into 14–24 weeks and 24–34 weeks), gestational age at the time of cerclage placement (entered as a continuous covariate), and the operating surgeon. The overall model fit and significance were evaluated using the Omnibus test. Adjusted hazard ratios (aHRs) were calculated, along with their corresponding 95% confidence intervals (CIs). A two-tailed p-value of less than 0.05 was considered statistically significant for all analyses

Results:

The baseline clinical characteristics and operative indications of the entire study population (n = 131) are summarized in Table 1.

Table 1: Baseline Characteristics and Operative Indications of the Entire Study Cohort

	n=131
Maternal Age (Years)	31 (18 - 44)
Prior PTB History (14-20 wk)	57 (43.5%)
Prior PTB History (20-24 wk)	15 (11.5%)
Prior PTB History (24-34 wk)	30 (22.9%)
Gestational Age at Cerclage Placement (Days)	125 (85 - 185)
Cerclage History	
• No Cerclage History	92 (70.2%)
• 1 Prior Cerclage	35 (26.7%)
• 2 or More Prior Cerclages	4 (3.1%)
Indication of Cerclage	
• History-indicated	60 (45.8%)
• Ultrasound-indicated (USG)	10 (7.6%)
• Examination-indicated	61 (46.6%)

Note: Data were expressed as median(minimum-maximum) and n(%).

The median maternal age of the cohort was 31 years (range, 18–44 years). With respect to obstetric history, 43.5% of patients had a prior preterm birth or pregnancy loss between 14 and 20 weeks of gestation, whereas 11.5% and 22.9% had a history of preterm birth between 20–24 and 24–34 weeks, respectively. The median gestational age at cerclage placement was 125 days (range, 85–185 days).

Regarding prior cerclage experience, 70.2% of patients underwent their first cerclage, 26.7% had a history of 1 prior cerclage, and 3.1% had undergone 2 or more prior cerclage procedures. In terms of operative indications, examination-indicated cerclage was the most frequently encountered indication, accounting for 46.6% of cases, followed closely by history-indicated cerclage (45.8%). Ultrasound-indicated cerclage represented the smallest subgroup, comprising 7.6% of the study population.

A comprehensive comparison of maternal demographic characteristics, baseline obstetric history, operative parameters, and clinical outcomes between patients who received long-term indomethacin therapy and those who underwent standard short-term perioperative management is presented in Table 2.

Table 2: Clinical Characteristics and Pregnancy Outcomes According to Long-Term Indomethacin Administration

	No Long-Term Indomethacin (n=77)	**Long-Term Indomethacin (n=54)**	***p-value***
Maternal Age (Years)	31 (18 - 44)	31 (22 - 43)	0.272
Prior PTB History (14-20 wk)	34 (44.2%)	23 (42.6%)	0.859
Prior PTB History (20-24 wk)	7 (9.1%)	8 (14.8%)	0.311
Prior PTB History (24-34 wk)	21 (27.3%)	9 (16.7%)	0.155
Gestational Age at Cerclage (Weeks)	17 (12 - 26)	19 (13 - 25)	0.083
Cerclage History			0.201
• No Cerclage History	58 (75.3%)	34 (63%)	
• 1 Prior Cerclage	18 (23.4%)	17 (31.5%)	
• 2 or More Prior Cerclages	1 (1.3%)	3 (5.6%)	
Cervical Dilation at admission	6 (8%)	8 (15.1%)	0.205
Cerclage Suture Type			**0.040**
• Prolene / Ethibond	20 (26.0%)	6 (11.3%)	
• Mersilene Tape	57 (74.0%)	47 (88.7%)	
Long-Term Indomethacin Duration (Days)	–	38 (3 - 118)	–
Postcerclage Abortion	8 (10.4%)	7 (13%)	0.649
Gestational Age at Delivery (Weeks)	37 (18 - 40)	34 (18 - 40)	**0.009**
Spontaneous PTB <37 Weeks	28 (36.4%)	31 (57.4%)	**0.017**
Spontaneous PTB <34 Weeks	14 (18.2%)	15 (27.8%)	0.193
Clinical Chorioamnionitis	5 (6.5%)	3 (5.6%)	1.000
Cause of Delivery			**0.026**
PPROM	18 (23.3%)	26 (48.1%)	
Spontaneous Preterm Labor	36 (46.7%)	19 (35.1%)	
Prior Cesarean Section	9 (11.6%)	2 (3.7%)	
Chorioamnionitis	1 (1,2%)	1 (1.8%)	
Malpresentation	1 (1.2%)	1 (1.8%)	
Birth Weight (Grams)	2900 (180 - 5004)	2390 (200 - 4000)	**0.021**
Latency Period (Days)	123 (0 - 186)	94 (10 - 175)	**0.005**

Note: Data were expressed as median(minimum-maximum) and n (%).

PTB: preterm birth PPROM: prterm premature rupture of membranes

Maternal age (p=0.272), prior history of preterm birth at 14–20 weeks (p=0.859), 20–24 weeks (p=0.311), and 24–34 weeks (p=0.155), as well as gestational age at cerclage placement (p=0.083), were comparable between the two groups. Similarly, no statistically significant differences were observed regarding cerclage history (p=0.201), cervical dilation or prolapsed membranes at presentation (p=0.205), post-cerclage abortion rates (p=0.649), clinical chorioamnionitis (p=1.000), or spontaneous preterm birth before 34 weeks of gestation (p=0.193), suggesting generally comparable baseline clinical characteristics between groups.

A significant difference was observed in the type of cerclage suture used. Mersilene tape was more frequently used in patients who subsequently received long-term indomethacin therapy compared with those managed without long-term treatment (88.7% vs. 74.0%, p=0.040), corresponding to a small-to-moderate association (φ=0.180). As expected, according to study-group allocation, patients in the long-term treatment group received indomethacin for a median duration of 38 days (range: 2–118 days).

Regarding pregnancy outcomes, patients receiving long-term indomethacin delivered at a significantly lower gestational age than those who did not receive prolonged treatment (median 34.0 vs. 37.0 weeks, p=0.009), with a small-to-moderate effect size (r=0.23). Consistent with this finding, spontaneous preterm birth before 37 weeks occurred more frequently in the long-term indomethacin group (57.4% vs. 36.4%, p=0.017), demonstrating a moderate association (φ=0.21). Furthermore, the distribution of delivery indications differed significantly between groups (p = 0.026; Cramer's V = 0.282). Post-hoc comparisons showed that preterm premature rupture of membranes (PPROM) was significantly more common in the long-term indomethacin group (53.1% vs. 27.7%, p < 0.05), whereas no significant differences were observed for the remaining delivery indications (all p > 0.05).

Neonatal birth weight was significantly lower in the long-term indomethacin group than in the comparison group (median 2390 g vs. 2900 g, p=0.021), with a small-to-moderate effect size (r=0.20). Finally, the interval between cerclage placement and delivery was significantly shorter in patients receiving long-term indomethacin (median 94 vs. 123 days, p=0.006), corresponding to a small-to-moderate effect size (r=0.24).

To evaluate the primary outcome of pregnancy prolongation, Kaplan–Meier survival analysis was performed to compare the latency period (defined as the interval from cerclage placement to delivery) between the two study groups. The cumulative probability of remaining undelivered over time differed significantly with long-term indomethacin exposure (p < 0.001, Figure 1). Patients who did not receive long-term indomethacin exhibited a significantly longer latency period than those receiving prolonged treatment. The median latency duration was 123.0 days (95% CI: 98.48–147.52) in the no long-term indomethacin group compared with 94.0 days (95% CI: 72.60–115.40) in the long-term indomethacin group. Across the entire cohort, the median latency period was 107.0 days (95% CI: 94.44–119.56), while the mean latency period was 105.77 days (95% CI: 97.06–114.48).

To evaluate the impact of long-term indomethacin administration on pregnancy duration, an independent-samples Mann–Whitney U test was performed. A significant difference was observed between the treatment groups (p = 0.009). Patients who did not receive long-term indomethacin exhibited a longer gestational duration, with a median delivery time of 259.0 days (range, 126.0–284.0), compared with 240.0 days (range, 127.0–283.0) among patients receiving prolonged indomethacin treatment. The magnitude of this difference was small to moderate (r = 0.23).

The association between long-term indomethacin use and spontaneous preterm birth before 34 weeks of gestation was subsequently examined using contingency table analysis. In the no-long-term indomethacin group, 14 of 77 patients (18.2%) delivered before 34 weeks, compared with 15 of 54 patients (27.8%) in the long-term indomethacin group, and this difference did not reach statistical significance (p = 0.193).

To evaluate the independent association between long-term indomethacin administration and pregnancy latency, a multivariable Cox proportional hazards regression model was constructed, adjusting for cerclage indication, prior mid-trimester loss and preterm birth history, gestational age at cerclage placement, and operating surgeon. The overall model was statistically significant (Chi-square = 92.889, df = 10, p <

0.001).

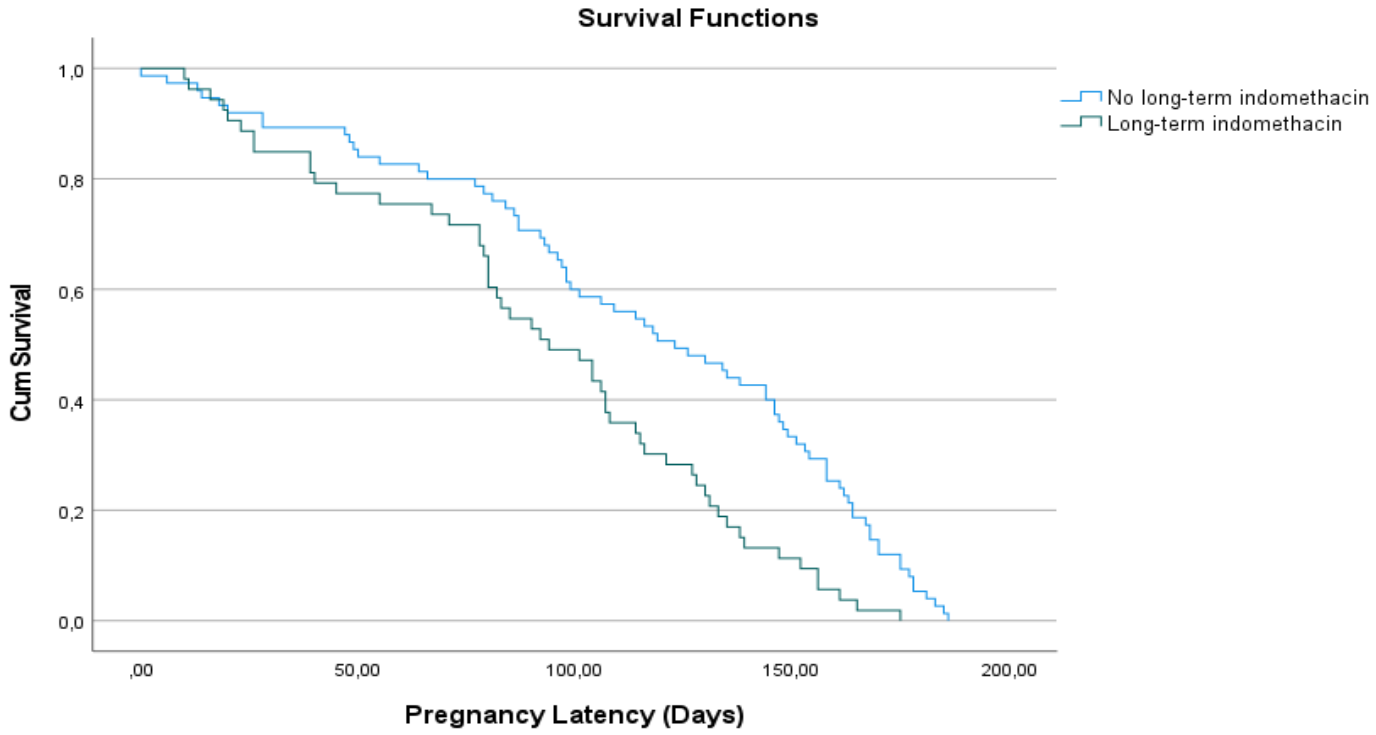

Figure 1: Kaplan-Meier survival analysis of pregnancy latency (days from cervical cerclage placement to delivery) stratified by long-term indomethacin administration.

Cerclage indication remained independently associated with pregnancy latency. Compared with examination-indicated cerclage, patients undergoing history-indicated cerclage demonstrated a significantly lower hazard of delivery (adjusted hazard ratio [aHR] = 0.510, 95% CI: 0.276–0.944, p = 0.032). In contrast, ultrasound-indicated cerclage was not significantly associated with latency duration (aHR = 0.734, 95% CI: 0.354–1.522, p = 0.406).

Gestational age at the time of cerclage placement was also independently associated with delivery timing. Each additional day of gestation at cerclage placement was associated with a 3.4% increase in the hazard of delivery (aHR = 1.034, 95% CI: 1.023–1.045, p < 0.001).

Neither prior pregnancy loss/preterm birth history between 14–24 weeks (aHR = 1.053, 95% CI: 0.673–1.646, p = 0.821) nor between 24–34 weeks (aHR = 1.115, 95% CI: 0.653–1.903, p = 0.691) was independently associated with pregnancy latency. Similarly, the operating surgeon was not a significant predictor of delivery timing (overall p = 0.791).

After adjustment for all covariates included in the model, long-term indomethacin administration remained significantly associated with an increased hazard of earlier delivery (aHR = 1.728, 95% CI: 1.116–2.677, p = 0.014).

Discussion:

Cervical cerclage remains one of the most effective interventions for the prevention of spontaneous preterm birth in selected high-risk pregnancies. Current guidelines recommend cerclage for women with a singleton pregnancy, a history of spontaneous preterm birth, and a short cervix identified by transvaginal ultrasonography [1-3]. In addition, emergency cerclage may be considered in women presenting with painless cervical dilatation and exposed or prolapsed fetal membranes before fetal viability. These patients represent a particularly high-risk population, as severe preterm birth and pregnancy loss are common in the absence of intervention.

Previous studies have reported success rates of 60–80% following emergency cerclage, with pregnancy prolongation ranging from approximately 4 to 7 weeks. However, outcomes remain highly variable, reflecting differences in patient characteristics, cervical status at presentation, and the presence of underlying inflammatory or infectious processes.

Increasing evidence suggests that cervical shortening, cervical dilatation, and intra-amniotic inflammation represent a continuum of disease progression leading to spontaneous preterm birth [10]. Consequently, adjunctive therapies aimed at reducing inflammation have been proposed as potential strategies to improve cerclage outcomes.

Indomethacin is frequently administered perioperatively because of its anti-inflammatory and prostaglandin-inhibitory effects [9,10]. Nevertheless, evidence supporting prolonged administration after cerclage placement remains limited. The present study was undertaken to address this knowledge gap and evaluate whether extending indomethacin treatment beyond the immediate perioperative period is associated with improved pregnancy latency and reduced preterm birth rates.

In the present study, women who received prolonged indomethacin therapy delivered at an earlier gestational age and experienced higher rates of spontaneous preterm birth before 37 weeks and PPROM compared with those who received standard-duration treatment. Furthermore, Kaplan–Meier analysis demonstrated a significantly shorter latency period from cerclage placement to delivery in the prolonged-treatment group. Importantly, this association persisted after adjustment for clinically relevant covariates in the multivariable Cox regression model, where prolonged indomethacin use remained independently associated with an increased hazard of earlier delivery.

The biological rationale for prolonged indomethacin administration is supported by evidence suggesting that inflammation and prostaglandin-mediated pathways contribute to cervical remodeling and preterm birth. In a retrospective cohort of women with a singleton pregnancy and a short cervix managed with long-term indomethacin therapy, Seif et al reported stabilization or improvement in cervical length in approximately two-thirds of patients, while the majority delivered beyond 32 weeks of gestation [11]. These findings suggest that prolonged cyclooxygenase inhibition may attenuate progressive cervical shortening in selected high-risk pregnancies and provide a theoretical basis for extending treatment beyond the perioperative period.

The available evidence regarding adjunctive indomethacin administration at the time of cervical cerclage remains limited and somewhat inconsistent. The landmark randomized controlled trial by Miller et al. demonstrated that perioperative cefazolin and indomethacin administration significantly increased the proportion of pregnancies remaining undelivered for at least 28 days following examination-indicated cerclage [10]. However, no significant differences were observed in gestational age at delivery or neonatal outcomes. Subsequently, Premkumar et al. reported similar findings in a retrospective cohort study, demonstrating improved gestational latency and higher birth weight among women receiving the same perioperative prophylactic regimen without an increase in chorioamnionitis rates [12].

In contrast, Young et al. were unable to reproduce the latency benefit in an external validation cohort [13]. Although the rate of pregnancy prolongation beyond 28 days was numerically higher among women receiving indomethacin and cefazolin, the association was no longer significant after adjustment for confounding variables. Interestingly, the authors observed a substantial reduction in intra-amniotic infection among treated patients, suggesting that perioperative anti-inflammatory and antimicrobial therapy may influence infectious morbidity even when a measurable latency benefit is not observed [13].

Taken together, these studies suggest that short-term perioperative indomethacin administration may provide benefit in selected patients undergoing examination-indicated cerclage. However, the available literature has focused almost exclusively on immediate perioperative treatment, and evidence regarding prolonged indomethacin administration beyond the perioperative period remains scarce. In contrast to the favorable findings reported with short-term administration [10,12,13] our results did not demonstrate a benefit of extended treatment and suggest that any potential advantage of indomethacin may be limited to the immediate perioperative period.

This finding should be interpreted with caution because prolonged indomethacin therapy was not randomly assigned. In routine clinical practice, clinicians were more likely to continue indomethacin in women perceived to be at higher risk for spontaneous preterm birth, particularly those with shorter cervical length or more concerning clinical features. Although cervical length was not significantly different between groups,

women receiving prolonged therapy tended to have shorter cervices at presentation, suggesting the possibility of confounding by indication. To minimize this bias, we adjusted for clinically relevant baseline variables in the multivariable Cox regression analysis, and prolonged indomethacin therapy remained independently associated with a shorter latency to delivery. Nevertheless, residual confounding inherent to the retrospective design cannot be excluded, and causality cannot be inferred.

Another factor that may have influenced the observed outcomes is the type of cerclage suture material. In our cohort, Mersilene tape was used more frequently among women who subsequently received prolonged indomethacin therapy. Surgical literature has long suggested that braided sutures may be associated with a higher risk of bacterial colonization and infection compared with monofilament materials. Supporting this hypothesis, a prospective longitudinal study investigating cervical cerclage suture materials proposed that braided sutures may promote vaginal pathobiont colonization, leading to local inflammation and adverse cervical vascular remodeling [14]. Similarly, the COTS pilot trial and subsequent comparative studies have suggested that suture material and configuration may influence pregnancy outcomes through effects on microbial colonization, local inflammatory responses, and cervical tissue remodeling [15, 16]. Given that Mersilene tape was more frequently used in the prolonged indomethacin group, the potential contribution of suture material to the observed differences in pregnancy latency should be considered. Although our multivariable model adjusted for several clinically relevant confounders, suture material was not included in the final model, and therefore residual confounding related to cerclage material cannot be completely excluded.

Despite the biological plausibility of prolonged cyclooxygenase inhibition and the encouraging findings reported in other clinical settings [11,17], our study did not demonstrate a benefit of prolonged indomethacin administration following cervical cerclage. On the contrary, prolonged treatment was associated with a shorter latency period and an increased hazard of earlier delivery after adjustment for clinically relevant covariates. However, these findings should be interpreted with caution. Given the retrospective design and the non-random allocation of treatment duration, residual confounding cannot be completely excluded. It is possible that prolonged indomethacin therapy was preferentially administered to women perceived to be at greater risk for adverse pregnancy outcomes, a phenomenon commonly referred to as confounding by indication.

An important consideration when interpreting our findings is the potential for confounding by indication. In routine clinical practice, prolonged indomethacin therapy was not randomly assigned but was more likely to be prescribed to women perceived by the treating physician to be at higher risk of preterm birth, particularly those with more pronounced cervical shortening or other concerning clinical features. Therefore, the poorer outcomes observed in the prolonged-treatment group may, at least in part, reflect the underlying severity of disease rather than a detrimental effect of prolonged indomethacin itself.

Indeed, women receiving prolonged indomethacin generally presented with shorter cervical length at the time of cerclage placement, suggesting a less favorable baseline prognosis. Cervical shortening is a well-established predictor of spontaneous preterm birth, and this difference may have influenced subsequent pregnancy outcomes despite cerclage placement. Because treatment duration was determined by physician preference rather than protocol, selection bias and confounding by indication cannot be completely eliminated despite multivariable adjustment. To minimize this potential bias, we adjusted for clinically relevant baseline variables, including cerclage indication, gestational age at cerclage, previous spontaneous preterm birth, and operating surgeon in the multivariable Cox regression model. Even after adjustment, prolonged indomethacin therapy remained independently associated with a shorter latency to delivery. Nevertheless, residual confounding cannot be excluded because of the retrospective observational design, and causality cannot be inferred. Prospective randomized studies are required to determine whether prolonged indomethacin therapy itself influences pregnancy duration or merely reflects treatment selection in women with intrinsically higher baseline risk.

In conclusion, prolonged indomethacin administration following cervical cerclage was not associated with improved

pregnancy prolongation and remained independently associated with a shorter latency period from cerclage placement to delivery after adjustment for clinically relevant confounders. Although these findings do not support the routine continuation of indomethacin beyond the immediate perioperative period, prospective studies are needed to determine whether specific subgroups of women may benefit from extended anti-inflammatory therapy following cerclage placement.

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