



Predictors of cerclage failure in patients with singleton pregnancy undergoing prophylactic cervical cerclage

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Abstract

Purpose The role of cervical cerclage to prevent preterm birth (PTB) remains controversial. The aim of this study was to identify prognostic factors for cerclage failure among singleton pregnant women following prophylactic cerclage (PC).

Methods A retrospective analysis of PC was performed in a single center. The main outcome measure was cerclage failure, defined by spontaneous early PTB prior to 32 weeks' gestation. Age, BMI, history of instrumentation of the uterus, history of second trimester miscarriage, previous conization, positive vaginal swab prior cerclage, gestational age at time of cerclage, CRP 1 week after cerclage and post-cerclage US changes of cervical length were tested as predictive factors. Descriptive statistical and binary logistic regression analyses were performed.

Results 141 women underwent cerclage procedures between 2007 and 2016. 39 patients had PC with McDonald suture, singleton pregnancy and complete clinical follow-up information, thus fulfilling the inclusion criteria. Multivariate analysis showed that history of instrumentation of the uterus was the only independent prognostic factor [OR = 0.14 (0.03, 0.72) $p = 0.019$] for cerclage failure.

Conclusion This is the first study showing that a history of previous uterine instrumentation is an independent predictor of cerclage failure. This finding has significant clinical implications for women of childbearing age, particularly when management of miscarriage/abortion is being considered. Women should be informed about the potential risks when counseled prior to surgical evacuation and medical management or cervical ripening should be considered. These results are also helpful in counseling patients undergoing cerclage, when a prior uterine instrumentation has been performed.

Keywords Cervix · Ultrasound · Surgical techniques · Preterm birth · Cerclage

Introduction

First described by Shirodkar in 1955, cervical cerclage is not new to the obstetric tool belt; however, many clinical questions around its use remain unclear and work to demystify this practice continue in the medical literature [1]. Recognized indications for cerclage today include the following: (1) history-indicated (history of two or more late miscarriages or early preterm births), (2) ultrasound-indicated (short cervix in transvaginal ultrasound scan in women with prior preterm birth), and (3) physical examination based (cervical dilatation with visible bulging membranes).

Prophylactic cerclage is implemented in groups 1 and 2 and emergency cerclage in group 3 [2, 3].

Owing to the difficulties in setting up prospective randomized trials with adequate sample sizes and events, the data informing practice leaves clinicians generally divided on the matter of its effectiveness [4–6]. International guidelines advise caution in the use of this treatment option, suggesting that it can be used only in certain circumstances. Currently, it is practiced worldwide with varying frequency [2]. Information to identify predictive factors for the success of cervical cerclage remains an important area for research, particularly because early preterm birth (EPB) remains a persistent and growing obstetric problem and the leading cause of neonatal morbidity and mortality [7, 8].

The reported incidence of EPB worldwide ranges between 5 and 10% [9–11]. It is associated with a wide range of underlying etiologies. Medically indicated preterm deliveries constitute a significant though minor proportion

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and serve to benefit the mother or fetus, e.g., in intrauterine growth restriction. In contrast, the majority of preterm deliveries occur spontaneously, resulting from various pathological processes including premature rupture of membranes (PROM), intrauterine infection/inflammation, decidual hemorrhage, uterine anomalies, pathologic uterine distention, and cervical insufficiency [9]. Environmental factors such as stress, smoking, and heavy work are also known to be influential [2].

Objective data regarding predictors of success of prophylactic cerclage are still scarce. Serum C-reactive protein levels and post-cerclage ultrasonographic cervical length have been identified as predictors of success of prophylactic cerclage [12]. The purpose of our paper is to investigate the association of nine factors with the failure of cerclage, in order to have clinically useful predictive factors. This is assessed in terms of EPB events occurring in pregnancies following cerclage. This information will help clinicians in selecting patients more specifically and also aid in the counseling of patients.

Materials and methods

A retrospective cohort study was carried out assessing patients who had prophylactic cerclage over a 9-year period at the Department of Gynecology and Obstetrics, Inselspital University Hospital of Berne, Berne, Switzerland. The Department is a large tertiary unit and national referral center for fetomaternal medicine in Switzerland. Women who had undergone cerclage in pregnancy were located via the hospital database and records reviewed retrospectively for inclusion in the analysis.

During the period between 2007 and 2016, a total of 141 patients were found to have had cerclage. Indication for prophylactic cerclage included either a history of two or more late miscarriages or early preterm births (history-indicated) or a previous preterm birth and a short cervix < 25 mm in transvaginal ultrasound in the actual pregnancy. We excluded women with multiple pregnancies ($n = 11$), women with emergency cerclage ($n = 46$), women with missing data ($n = 36$), those who had to be delivered electively preterm for fetal complications ($n = 4$) and those who delivered at another department and thus were lost to follow-up ($n = 14$). This resulted in a patient population of 41 patients who underwent prophylactic cerclage. Two women were excluded from the study as they had a history of laparoscopic cerclage before pregnancy. The remaining 39 received transvaginal cerclage using the McDonald method and were eligible for analysis.

The outcome measure was EPB. Early preterm delivery was considered when delivery occurred < 32 weeks of gestation. Nine predictors of outcomes were tested in the

study group. These included: age; body mass index (BMI); history of previous uterine instrumentation following miscarriage; history of conization; history of second trimester miscarriage, bacterial infection at cervical swab before cerclage; C-reactive protein value (CRP) 1 week after cerclage; gestation at which the cerclage was performed; and ultrasonography modifications of cervical length (postC-US) at 10 days following cerclage. Any positive vaginal bacterial swab found within 4 weeks prior to cerclage was included. Patients with positive swabs were treated with antibiotic, according to sensitivities. A finding of Group B streptococcus (with negative urine culture) was also treated. All women received short-term tocolysis with indomethacin during and after the cerclage.

Certified operators performed all ultrasound examinations and cervical length measurements were performed according to the international recognized standards. The shortest of at least three measurements was documented and used in the analysis.

Statistical analysis

Descriptive statistical and binary logistic regression analyses were performed. The student *t* test and Mann–Whitney *U* test were used to compare continuous parametric and nonparametric variables, respectively. Univariate and multivariate analysis was performed to analyze factors predicting outcomes. Multivariable models were carried out for variables reporting a *p* value ≤ 0.3 in univariate analysis. *p* values ≤ 0.05 were considered statistically significant. Statistical analysis was performed with GraphPad Prism version 6.0 (GraphPad Software, San Diego CA, USA) and IBM-Microsoft SPSS version 22.0.

Ethical approval

Ethical approval for the current study (Study number: 3037) was obtained on the 01.06.2016 by the local institutional review board (Ethics Committee of the Canton of Bern, Switzerland).

Results

Thirty-nine patients aged between 20 and 39 years were included in the analysis. The median age of the study cohort was 33 (range 20–39) years and the median BMI was 25 (range 18–38). Five out of forty-one (12%) pregnancies were a result of in vitro fertilization and 36 (88%) were spontaneous pregnancies. The median gestation of cerclage performed during pregnancy was 18 weeks and 5 days (9 + 3 to 24 + 6); two women had laparoscopic cerclage before pregnancy. The median cervical length was 15 (5–42) mm

prior to cerclage and the median change in cervical length after cerclage was 19.4 (7–45) mm. Twenty seven of the 39 (41%) women included in the analysis had history-indicated cerclage and 14/39 (36%) had ultrasound-indicated cerclage. Positive swabs included bacterial vaginosis and were treated prior to cerclage. Swabs positive for abnormal bacteria were treated as per hospital protocols. All patients' characteristics have been reported in Table 1.

Three of the 39 women experienced preterm PROM before 24 weeks. Seventeen of the 39 (44%) women delivered at less than 32 weeks of gestation, 2/39 (5%) between 32 and 34, and 21/39 (54%) delivered after the 34 weeks of gestation. Mode of delivery was evenly distributed between vaginal in 17/39 (44%) patients and 22/39 (56%) caesarian births. Indications for caesarian delivery included early gestation at delivery (< 30 weeks of pregnancy), previous myomectomy, previous cesarean section or pre-eclampsia. All pregnancy outcome measures after prophylactic cerclage have been reported in Table 2.

Univariate analysis of the potential prognostic factors affecting the time of delivery found age (OR 1.13 95% CI 0.95–1.34, $p = 0.15$), history of instrumentation of uterus (OR 0.14 95% CI 0.03–0.72, $p = 0.02$), and ultrasound modification of cervical length at 10 days after cerclage (OR 0.97 95% CI 0.91–1.04, $p = 0.48$) to be the only variables eligible for the multivariate analysis. Among them, only a history of previous uterine instrumentation was found to be an independent prognostic factor for EPB at the multivariate analysis (Table 3).

Table 2 Pregnancy outcome after prophylactic cerclage

Median week at delivery, week/ days (range)	35 weeks + 6 days (20 weeks + 3 days – 40 weeks)
PROM (%)	3/39 (8%)
Delivery timing	
< 32	18/39 (46%)
32–34	2/39 (5%)
> 34	21/39 (54%)
Type of delivery	
Vaginal delivery (%)	22/39 (56%)
Cesarean section (%)	19/39 (49%)
Median fetal weight, g (range)	2430 (500–3610)

Discussion

The role of cervical cerclage to prevent preterm birth remains controversial. Despite its long history in obstetrics, there have only been two randomized, controlled trials assessing prophylactic cerclage and their sample sizes small [7, 13, 14]. Extracting the maximal amount of information from observational studies and, specifically, identifying predictive factors for the success of cervical cerclage remains an important area of research which can help to guide clinicians as well as to inform patients [16].

Previous studies have shown that the post-cerclage cervical length is predictive of delivery before 32 weeks in the setting of prophylactic cerclage [15]. Women in whom cervical length was shorter than 25 mm had a significant likelihood of delivery before 32 weeks' gestation (OR 0.4, 95% CI 0.17–0.92 $p = 0.021$) [15]. Guzman et al. also described findings from 29 cases of ultra-sound indicated cerclage [16]. This study showed that cerclage resulted in a significant lengthening of the cervix as well as predicting delivery

Table 1 Patients characteristics

Median Age (range)	33 (20–39)
Median BMI (range)	25 (18–38)
History of conization (%)	5/39 (13%)
History of instrumentation of uterus (%)	16/39 (41%)
History of II trimester miscarriage (%)	36/39 (92%)
Cerclage Indication:	
> 2 late miscarriage (%)	27/39 (69%)
US < 2.5 cm cervical length + at least 1 previous miscarriage/early preterm delivery (%)	14/39 (36%)
Median GA at the cerclage, week + days (range)	18.5 (9 weeks + 3 days – 24 weeks + 6 days)
Positive cervical swabs prior to cerclage (%)	10/39 (26%)
Median CPR value after cerclage (range)	3 (3–24)
Median cervical US length at time of cerclage, mm (range)	15 (5–42)
Median cervical US length 10 days after cerclage, mm (range)	19.4 (7–45)

Table 3 Univariate and multivariate analysis of factors associated to early preterm delivery after prophylactic cerclage (all patients, $n = 39$)

	Early preterm delivery			
	Univariate analysis		Multivariate analysis	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Age	1.11 (0.96, 1.29)	0.132	1.14 (0.96, 1.35)	0.123
BMI	0.96 (0.86, 1.09)	0.590		
History of conization (yes/no)	0.83 (0.12, 5.60)	0.851		
History of instrumentation of uterus (yes/no)	6.50 (1.46, 28.80)	0.014	0.13 (0.02, 0.67)	0.015
Cervical swabs prior to cerclage (pos/neg)	1.38 (0.33, 5.78)	0.656		
History of II trimester miscarriage (yes/no)	1.20 (0.17, 8.07)	0.851		
CPR value after cerclage	0.91 (0.76, 1.09)	0.333		
GA at the cerclage	0.92 (0.78, 1.08)	0.320		
Delta US at 10 days after cerclage	0.96 (0.92, 1.01)	0.192	0.98 (0.92, 1.04)	0.633

Multivariable models were carried out for variables reporting a p value ≤ 0.2 in univariate analysis

before 36 weeks of gestation [16]. They describe that a post-cerclage cervical length < 10 mm was predictive of delivery before 36 weeks' gestation with a positive predictive value of 70.6% [16]. A more recent study assessing the rate of shortening, as measured by transvaginal ultrasound, also found a positive association [17]. In this study, a rate of shortening of 1 mm/week was associated with a 59% risk of preterm delivery [17]. In our study, cervical length within 10 days post-prophylactic cerclage was not associated with gestation at delivery. According to our results, routine ultrasound in the first 10 days after cerclage in the absence of clinical change is not effective in terms of predictive value. This finding is consistent with the results from the study by Owen et al. [18]. The findings from this randomized control trial showed that post-cerclage cervical length obtained by transvaginal ultrasound is a poor predictor of gestational age [18].

It is noted that the increase in cervical length following cerclage in this study is lower than that reported by other studies [15, 17–19]. This may be explained by the heterogeneity between the study designs and study populations. In some studies, the post-cerclage cervical length was measured within 72 h of cerclage [19], whereas in others cervical length was a pooled measurement according to the gestational age [15, 17, 19]. It can be seen that with a prolonged period between cerclage and measurement of the cervix, the increase in cervical length is also less and closer to the findings of this study [19]. The proportion of USS indicated versus history indicated prophylactic cerclages also differ between the studies, and cervical lengths prior cerclage also range significantly. For example, in Song et al. the cervical length before cerclage was 30.2 mm (95% CI 10.0–52.5), whereas in our study this was approximately 10 mm shorter. Lastly, due to the variation in clinical presentations, the studies describe great variation in surgical methods applied; some cohorts describe outcomes predominantly

following Shirodkar technique [19], and others Laparoscopic or McDonald [8, 13, 16, 17].

Only one study of 44 women looked specifically at the utility of CRP as a biomarker in predicting success of prophylactic cerclage. Pre- and post-cerclage, CRP was significantly lower among women who delivered after 34 weeks (pre-cerclage CRP, 1.1 ± 1.0 vs. 11.4 ± 6.2 mg/dL, $p < 0.001$; post-cerclage CRP, 0.6 ± 0.5 vs. 7.4 ± 7.2 mg/dL, $p < 0.001$) [12].

In our study, previous history of uterine instrumentation was the only factor associated with delivery before 32 weeks gestation. There was no significant association with women who had a history of second trimester miscarriage. This suggests that it is the instrumentation of the uterus itself that determines cerclage outcome rather than its indication. A possible explanation of this may be that instrumentation of the cervix weakens the structural support, which may in turn lead to an increased likelihood that the mechanical barrier, protecting against ascending pathogens, is compromised with increasing gestational age despite placement of a suture. This potential association highlights the need for caution in the use of surgical uterine evacuation in the management of both miscarriage and procedures, whereby the cervix is manually dilated. In women of reproductive age, the need to explore safer surgical techniques (such as cervical ripening) or alternate management is of high importance. A recent meta-analysis assessed whether history of uterine evacuation involving mechanical dilatation of the cervix is associated with an increased risk of preterm birth. This meta-analysis found that women who had a history of at least one previous uterine instrumentation in the treatment of miscarriage and termination of pregnancy had an increased the risk of subsequent preterm birth before 32 weeks (OR = 1.69, 95% CI 1.20–2.38) [20]. This association was even higher for early preterm birth before 28 weeks, particularly in women with a history of more than

one uterine evacuation [20]. To our knowledge, this has not yet been shown specifically in the context of cerclage. Uterine instrumentation more than other variable can affect the outcome of the pregnancy and warrants further research. This information also serves as a caution to clinicians in the use of surgical uterine evacuation in the management of miscarriage. Owing to the limitations of our study (its retrospective design and limited small sample size), we cannot definitively answer the question whether surgical instrumentation of uterus after miscarriage should be avoided and that medical methods should be preferentially performed, but our results point in this direction. Furthermore, the possibility of a type-1 error cannot be ruled out. More research is needed to investigate this relationship further. Appropriate counseling of women includes not only potential benefits of cerclage based on prophylactic indication, but also—if preterm birth becomes imminent—advantages of early intrauterine transfer to a perinatal center, possibilities of tocolysis and antenatal corticosteroids, and guidance regarding the impact of the mode of delivery [21, 22].

Conclusion

Our study found for the first time that history of previous instrumentation of the uterus is the only independent predictive factor for EPB after a prophylactic cerclage. The study is limited by size and wider investigation, through multi-center cohorts, would inform the strength of this association. Nevertheless, these data indicate that caution is required in the use of standard surgical evacuation of late miscarriage, given that many women eligible for prophylactic cerclage have such history. These results are also helpful in counseling patients about the efficacy of prophylactic cervical cerclage as well as in management of their further pregnancy after the procedure.

Author contributions Protocol/project development: DS and DB, Data collection or management: KT, Data analysis: MLG, Manuscript writing/editing: KT, DS, DB and MLG

Compliance with ethical standards

Conflict of interest Author 1, K Taghavi, declares that she has no conflict of interest. Author 2, ML Gasparri declares that she has no conflict of interest. Author 3, D Bolla, declares that he has no conflict of interest. Author 4, D Surbek, declares that he has no conflict of interest.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee as well as the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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