

# Effectiveness of Cervical Cerclage on Preterm Delivery and Neonatal Outcome in Twin Pregnancies: Propensity Score Matching Analysis

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## Abstract

**Background:** The effectiveness of cervical cerclage (CC) in mothers suffering cervical incompetence (CI) for preventing preterm birth (PTB) in twin gestations remains controversial. Some studies show that it plays a preventive role in the occurrence of PTB, while others suggest it is ineffective.

**Objectives:** Our aim was to evaluate the effectiveness of CC in preventing PTB and negative neonatal outcome (e.g., respiratory distress syndrome (RDS) and birth weight) based on a new statistical framework: multilevel analysis and propensity score matching (PSM) in twin pregnancies.

**Methods:** A cross-sectional study was conducted in the maternity wards of three general and teaching hospitals in Tehran, Iran, during January 2014 to February 2015. Using stratified random sampling with the proportional allocation method, twin pregnancies were randomly selected from the medical files list. Of 431 eligible individuals, 31 patients underwent CC as a result of CI, and the others had healthy cervixes and no CC. Next, variables that confound the relationships between CC and PTB (e.g., assisted reproductive technology (ART), preterm rupture of membrane (PROM), nulliparous, history of abortion, and mother's age) by applying 1:2 PSM were matched in both groups. The CC group was considered the case group and, based on PSM, 61 patients, whose characteristics were similar to the CC group, were selected from 400 healthy mothers as a control group. For considering twins dependencies, multilevel modeling was used, and prevalence of PTB, LBW, and RDS, as well as mean gestational age in the two groups, were compared.

**Results:** The standardized mean difference (SMD) shows that the distribution of confounding variables in the propensity-matched data is the same in both groups. Results revealed that, although gestational age in the case group was significantly less than the control group, the prevalence of PTB in case and control was not significantly different ( $P = 0.190$ ). The prevalence of neonatal outcome of RDS and LBW in the case and control groups was not significant ( $P > 0.05$ ).

**Conclusions:** It appears that CC has an effective role in prevention of PTB, LBW, and RDS, because their prevalence in both groups was the same. However, drawing a clear conclusion regarding its role requires more research with a random clinical trial (RCT) design.

**Keywords:** Cervical Cerclage, Cervical Incompetence, Twin Pregnancies, Multilevel Modeling, Propensity Score

## 1. Background

The twin birth rate in the USA has increased dramatically during the last three decades, from 18.9 to 33.3 per 1,000 births between 1980 and 2009. During these years, the twin birth rate rose 76% (1) and, in 2013, reached 33.7 per 1,000 total births (2), primarily because of the increasing use of ART (3). The risk of LBW in twins is ten times more than for singletons (4). Prematurity is one of the most important factors that can cause mortality, long-term neurodevelopmental impairment, and prenatal morbidity (5), and has a significant effect on LBW (6, 7). In the first months after birth, twins' chances of dying are five times higher than singletons (8). Nearly 25% of very low birth weight infants (less than 1,500 g) and 16% of deaths occurring during the first six months of life are twins (9). The mean gesta-

tional age in twin pregnancies is almost three weeks less than singletons (9), and the risk of PTB is just a little less than 13 times as much as singletons. The rate of PTB is 56.6% vs. 9.7% in twins and singletons, respectively (2). Preterm infants are significantly more at risk of serious neonatal morbidities (10).

PTB is multifactorial, and one of these factors is cervical incompetence. The rate of cervical incompetence is reported between 0.1% and 2% and estimated as the cause of 15% of the recurrent pregnancy losses between 16 and 28 weeks (11). Cervical cerclage (CC) is a traditional treatment for preventing PTB (12, 13). It has been used for at least 50 years, having been introduced by Shirodkar (14), while McDonald improved upon its effectiveness (15). CC has some complications, such as bleeding, infection, and preterm premature rupture of membranes (PPROM), and

it may affect future pregnancies (13). A study by Newman demonstrated the risks of prematurity associated with a shortened cervical length in twin gestations not reduced by midtrimester cerclage (16).

Some studies show that CC decreases the probability of preterm delivery (17, 18). On the other hand, some researchers report that, in patients with a short cervix, the rate of spontaneous preterm delivery is not reduced by CC. One such review article reports there is no evidence to suggest CC is effective at preventing PTB or reducing prenatal deaths or neonatal morbidity in twin pregnancies (19).

## 2. Objectives

The aim of our study was to examine CC's effectiveness in preventing preterm delivery. The secondary aim was to evaluate CC's role in neonatal outcome (e.g., RDS and birth weight) in twin pregnancies by comparing a cervical incompetence (CI) group that had cerclage with twin gestation pregnant women whose cervixes were healthy and who had not had a cerclage in a previous pregnancy by a new statistical framework: propensity score matching and multilevel analyzing.

## 3. Methods

A cross-sectional study was conducted in the maternity wards of three general and teaching hospitals (Najmieh hospital, Shahid Akbar Abadi Maternity hospital, and a hospital where authorized by Islamic Republic of Iran Air Force) in Tehran, Iran, during January 2014 to February 2015. First, a list of hospitals that contained maternity wards located in Tehran was obtained from the Health Ministry. Next, three hospitals were selected, and twin pregnancies were randomly selected from the medical files list, using stratified random sampling with the proportional allocation method.

The inclusion criteria were twin delivery at study time, mother's age less than 40 years, and twins who were diamniotic-dichorionic (DCDA). Mothers with severe diseases, such as cancer, active vaginal bleeding, prior cerclage placement, placenta previa, smokers, alcoholic mothers, and infants with genetic or major fetal anomaly, monochorionic-monoamniotic placentation, and twins with twin-to-twin transfusion syndrome (TTTS) were excluded. Of 447 considered samples, 16 were dropped as a result of the exclusion criteria (Figure 1). A total of 431 eligible files whose information was collected 31 patients (7.2%) because of cervical incompetence have been done CC (McDonald procedure), while the others (92.8%,  $n = 400$ ) had healthy cervixes. Based on propensity score matching (PSM), mothers' characteristics which confound the

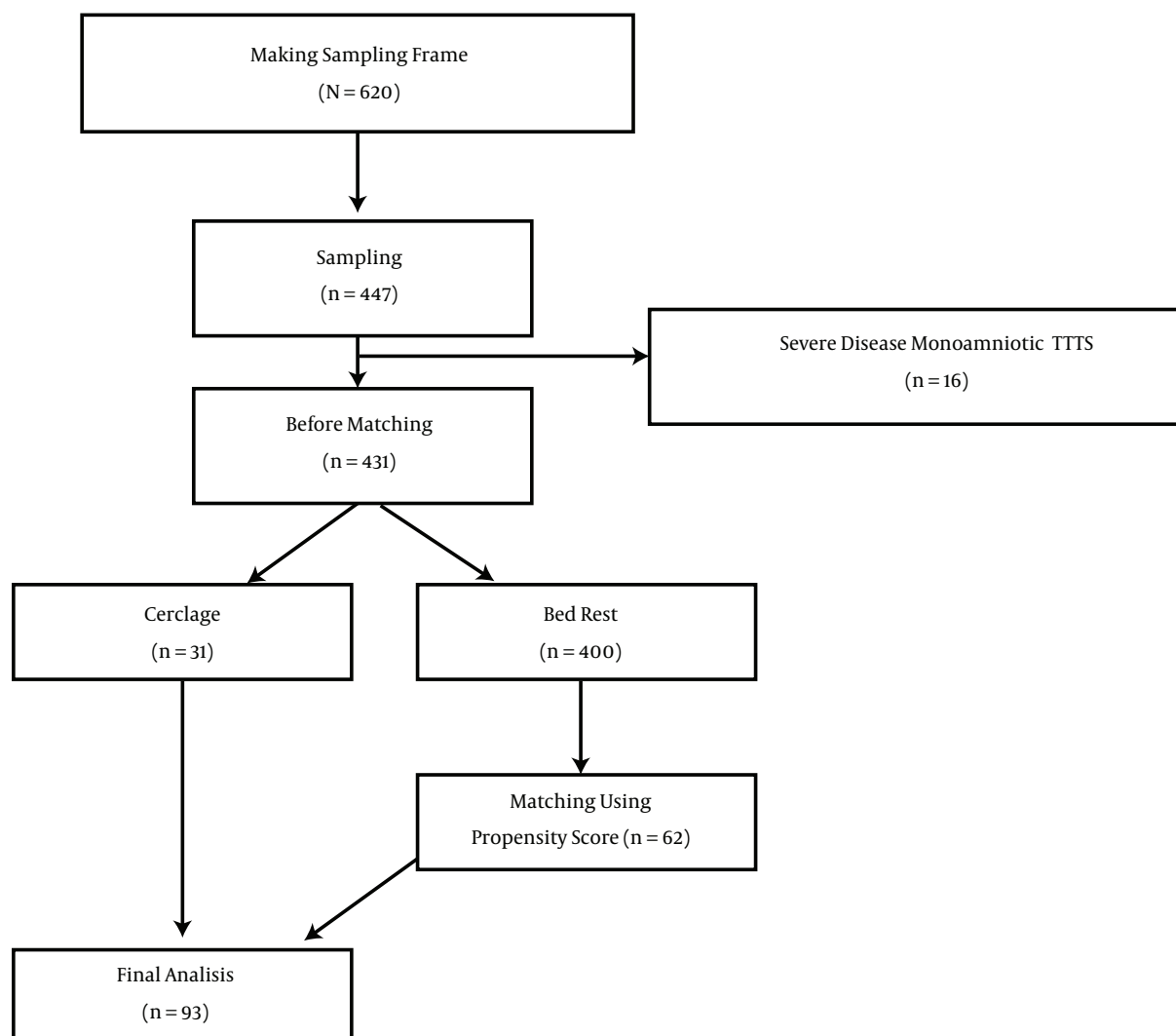
relationship between CC and PTB were matched in both groups. Thus, in the matched data, there were 31 patients who underwent CC and were considered a case group, and 61 patients, selected from 400 mothers with healthy cervixes and no cerclage in a prior pregnancy, were considered a control group.

Management styles and techniques for cerclage placement at the three institutions were exactly the same. The study protocol was approved by the Ethical Committee of the Medical School of Tarbiat Modares University. One researcher, using a man-made, validated checklist (CVI = 0.8, CVR = 0.77) gathered the data from the medical records. In this study, mothers who underwent cerclage surgery using the McDonald technique under spinal anesthetic in a "head down" position were considered a case group, and the others who had never had cerclage were allocated to the control group. Maternal information and information about the twin infants was collected by this checklist. The McDonald technique is used as a routine treatment for cervical incompetence in all three maternity wards because of its effectiveness and ease of placement (20). The primary outcome in our study was gestational age and incidence of PTB before 32 weeks' gestation. The secondary variables were neonatal outcome, including the prevalence of LBW and RDS.

### 3.1. Statistical Analysis

PSM was used to control confounding variables and treatment selection bias that may have been introduced by the mothers' characteristics. It provides probability that individuals would have been in a treatment group based on their pretreatment covariates. In other words, it transforms a multidimensional pretreatment confounder covariate to a one-dimensional variable as a result of the distribution of confounder covariates on average in case and control group is the same (21). In the first step, factors that possibly make treatment choice decisions, but do not influence the outcome, should not be included in estimating the propensity score (22). Thus, in order to distinguish potential confounders, cerclage treatment was considered a dependent variable and the following variables as independent variables: age, BMI, use of ART (e.g., IVF, IUI), and history of previous abortion, and a logistic model was fitted (21). In this step, in order not to miss any important confounder variables, type one error was set to 0.15. Next, the propensity score, based on significant variables, was calculated, and matching was done. A total of 31 patients from the case group were matched by applying a 1:2 propensity score matching (PSM) ratio using the nearest neighbor method.

For evaluating PSM, to reduce bias, prognostic score-based balance measures should be considered (23). Stan-



**Figure 1.** Study Follow Diagram

standardized bias, or standardized mean difference (SMD), which is the most common metric as a balance measure, has been proposed (23). The cut-offs for satisfactory standardized biases 0.1 or 0.25 are suggested, and larger values indicate groups are too different to compare in order to assess treatment effect (24). One advantage of SMD is that it is not affected by sample size (25).

Mothers' pretreatment characteristics, with respect to cerclage treatment, were compared by using Student's t-test for continuous variables and the chi-square test for categorical variables. All P values are two-sided. To evaluate the effect of cerclage upon the neonatal outcome in infants, since twins are dependent on each other, multi-level analyzing was used (26, 27). Each twin is nested in the

mother, thus newborns and mothers are considered level 1 and level 2, respectively. Restricted iterative generalized least square (RIGLS) was applied for fitting the model. The significance of the fixed effects was tested by F-statistic, and its degrees of freedom were computed using the containment method. In order to test the proportion of total variance that is attributed to the cluster level, the Inter-Class Correlation (ICC) was used. Normality of the latent random effect ( $u$ ) and error term ( $\varepsilon$ ) was investigated by the Kolmogorov-Smirnov test (KS-test). Furthermore, the significance level was set to 0.05. All analyses were done using R software, version 3.1.3, and Mlwin, version 2.1.

#### 4. Results

The results revealed that history of abortion, nulliparous, assisted reproductive technology, preterm rupture of membranes, and mother's age confound the relationships of cerclage and preterm delivery. In order to make both groups homogenous, PSM was used. Before applying PSM, the mean of mothers' ages in the case group was significantly less than the control group. In the case group, the mean of mothers' ages was  $26.77 \pm 5.6$ , and in the control group, it was  $28.9 \pm 5.6$  ( $P < 0.05$ ). An SMD for mothers' ages of 0.398 was obtained. As a result, its distribution was not the same in both groups, while after applying PSM, the difference between mothers' ages was no longer significant ( $26.77 \pm 5.6$  vs.  $25.76 \pm 5.1$  in the case group and control group respectively;  $P = 0.366$ ). The characteristics of both groups, before and after PSM, are shown in [Table 1](#).

[Table 1](#) reveals that all confounder variables are well matched. According to SMD, the distribution of using ART and being nulliparous is considerably different in the case and control groups, but after matching, distribution became almost the same, and the SMD decreased after matching. Prevalence of PTB was 13.1% and 24.1% in the control group and case group, respectively ( $P = 0.19$ ).

In the control group, the mean gestational age was  $34.72 \pm 3.6$ , and in the case group, it was  $33.00 \pm 4.65$ , and the difference between them was statistically significant ( $P = 0.015$ ). To assess dependencies of the twin outcome, parameters of the variance model ( $\sigma v^2, \sigma u^2$ ) and ICC were calculated. Significant parameter of variance model revealed for considering dependencies multilevel modeling is appropriate. [Table 2](#) shows the summary of regression coefficient applying multilevel modeling for evaluating the association between CC, neonatal twin outcome, and ICCs.

According to [Table 2](#), although newborn infants in the control group were 80% more at risk for LBW, compared to the case group, it is not significant. ICC in neonatal outcomes, which shows the proportion of total variance that was attributed to the twin level share, is significant.

#### 5. Discussion

The aim of this study was to evaluate the effectiveness of CC in increasing gestational age and preventing PTB, LBW, and RDS by comparing mothers with cervical incompetence who have had CC and mothers with healthy cervixes in twin pregnancies. The results show that, in the case group, the mean gestational age was significantly less than the control group. Indeed, CC did not increase gestational age in mothers with CI as well as mothers whose cervix is healthy but an important point is that cerclage

can prevent very preterm delivery, which occurs at less than 32 weeks of gestation. The prevalence of PTB in both groups was almost the same, and is not statistically significant. A systematic review conducted to evaluate the effectiveness of elective cervical cerclage in PTB, in which only randomized trials were included, compared cervical cerclage with standard treatment without cerclage and showed that CC has a significant effect on preventing birth before 34 weeks' gestation (18). Sun ko showed that digital examination-indicated cerclage, compared with expectant management, has a significant effect on increasing gestation and decreasing neonatal morbidity (28). Results of a retrospective study by vetr showed that patients who have rescue cerclage have significantly worse outcomes in terms of prolongation of pregnancy compared to elective cerclage done on the basis of history without objective evidence of cervical change and emergency cerclage with objective manifestation of cervical insufficiency (29).

A study designed to evaluate the efficacy, safety, and outcomes of midtrimester cerclage in patients carrying twins revealed that therapeutic cerclage might be beneficial for patients with advanced cervical changes (30). However, this study suffered from lack of sufficient sample size, with only 14 patients investigated. The results of another study revealed that, in women suffering emergency cervical incompetence, cervical cerclage played an effective role in prolonging pregnancy and improving neonatal outcome (31). On the other hand, a study by Newman showed that cerclage placement, in twin gestations with a shortened cervical length of 25 mm as measured by ultrasound, was not able to significantly decrease prematurity (16). In a review article evaluating four studies, it was suggested that, overall, there is no evidence for the effectiveness of cerclage at reducing the preterm delivery rate. However, the sample size in two of the trials evaluated was too small to draw firm conclusions (32). In another retrospective study, conducted on twin and triplet pregnancies, incidence of spontaneous preterm delivery with cerclage, as compared to conservative treatment, was not seen (33). In their study, in all multiple pregnancies from 1996 through 2002 that underwent serial CL measurements, cerclages were placed via the modified Shirodkar technique. However, matching was not done. This weakness is addressed in our study by relying on propensity score analysis and the McDonald technique.

Our investigation reveals that cerclage is an effective treatment to prevent LBW in twin pregnancies, since the prevalence of LBW in both groups was not significant, and the chance of LBW delivery was the same for mothers suffering CI and having CC and mothers with healthy cervixes. However, the use of prophylactic cerclage to prevent LBW remains controversial. Abo-Yaqoub et al. reported that

**Table 1.** Mothers' Characteristics by CC Group, Before and After PSM

	Before PSM count (percent)				After PSM count (percent)			
	Case Group, n = 31	Control Group, n = 400	SMD	P	Case Group, n = 31	Control Group, n = 62	SMD	P
ART	8 (25.8)	27 (6.8)	0.528	< 0.0001	8 (25.8)	13 (21.0)	0.113	0.599
History of abortion	4 (12.9)	91 (22.8)	0.258	0.203	4 (12.9)	7 (11.3)	0.049	0.820
Nulliparous	22 (71.0)	176 (44)	0.562	0.004	22 (71.0)	48 (77.4)	0.146	0.497
PROM	6 (19.4)	53 (13.3)	0.164	0.341	6 (19.4)	9 (14.5)	0.128	0.550

Abbreviations: ART, Assisted Reproductive Technology; PROM, Preterm Rupture of Membranes.

**Table 2.** Comparison of Neonatal Outcomes in Case and Control Groups in the Propensity Matched Patients

Neonatal outcomes	Case Group, No. (%)	Control Group, No. (%)	Beta	S.E Beta	OR <sup>a</sup>	P	ICC, %
LBW	16 (25.8)	48 (38.7)	-0.597	0.411	0.550	0.07	45
RDS	5 (8.1)	8 (6.5)	0.241	0.713	1.272	0.375	36

<sup>a</sup>Control group considered as a reference category.

neonatal birth weight in women with emergency cervical cerclage after 20 weeks is increased significantly by CC (34), while another study, conducted in triplet pregnancies, failed to demonstrate a benefit of CC in preventing LBW (35).

Our study also demonstrated that, although the chance of RDS in the case group was almost 20% more than in the control group, the prevalence of RDS in both groups was not significant. CC has an effective role to play in preventing RDS and decreasing the prevalence of RDS in women with CI, as well as in mothers with healthy cervixes. Our results point in the same direction as a retrospective cohort study of asymptomatic twin pregnancies, in which cervical dilation equal to 1cm was identified at 16 - 24 weeks. A significant decrease in the RDS rate of the CC group was reported, compared to expectant management (36). Further, a review of three articles assessing CC's effectiveness at preventing RDS revealed no significant differences between the cerclage and no cerclage groups (19). It appears that RDS is a function of gestational age, and cerclage has an indirect effect on it. Therefore, further investigation about CC's role in preventing RDS requires more research.

Although it is clear that randomized controlled trial (RCT) is the most valid methodology for evaluating treatment efficacy, because of its disadvantages (e.g., cost, time-consuming, some ethical drawbacks) designing a study based on that is not ration (22). Our study was limited by its retrospective approach. Because observational data was used, treatment randomized assignment was not possible, which caused the data to be biased. To minimize

these biases, propensity score matching was used. However, the sample size was decreased after the matching (37), and the resulting penalty was a lack of randomized assignment. Previous research has suggested that matching according to the propensity score is more effective than stratification or covariate adjustment (38). Obviously, however, propensity score matching operates only on variables that are collected (39). In the medical records, some variables, such as cervical length and prior preterm delivery, were not recorded. Drawing firm conclusions about CC's effectiveness requires a large RCT, which is recommended for future investigation.

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