Original Article

Role of Cervical Cerclage and Vaginal Progesterone in the Treatment of Cervical Incompetence with/without Preterm Birth History

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Abstract

Background: Preterm birth (PTB) is the leading cause of perinatal morbidity and mortality worldwide, and its prevention is an important health-care priority. The cervical incompetence is a well-known risk factor for PTB and its incidence is about 0.1–2.0%, while there is no ideal optimum treatment recommended currently. The cervical incompetence causes about 15% of habitual abortion in 16–28 weeks. This study aimed to evaluate the effectiveness and safety of cervical cerclage and vaginal progesterone in the treatment of cervical incompetence with/without PTB history.

Methods: We retrospectively observed the pregnancy outcome of 198 patients diagnosed with cervical incompetence from January 2010 to October 2015 in Beijing Hospital. Among the 198 women involved, women who had at least one PTB before 32 weeks (including abortion in the second trimester attributed to the cervical competence) were assigned to the PTB history cohort, and others were assigned to the non-PTB history cohort. All women underwent cerclage placement (cervical cerclage group) or administrated with vaginal progesterone (vaginal progesterone group) until delivery. The outcomes of interest were the differences in gestational age at delivery, the rate of premature delivery, neonatal outcome, complications, and route of delivery between the two treatment groups.

Results: Among the 198 patients with cervical incompetence, 116 patients in PTB history cohort and 80 patients in non-PTB history cohort were included in the final analysis. In the PTB history cohort, cervical cerclage group had significantly longer cervical length at 2 weeks after the start of treatment (23.1 ± 4.6 mm vs. 12.4 ± 9.1 mm, $P = 0.002$), higher proportion of delivery ≥37 weeks' gestation (63.4% vs. 33.3%, $P = 0.008$), bigger median birth weight (2860 g vs. 2250 g, $P = 0.031$), and lower proportion of neonates whose 1-min Apgar score <7 (5.9% vs. 33.3%, $P = 0.005$), compared with vaginal progesterone group. No significant differences were found in other outcome measures between the two treatment groups. In the non-PTB history cohort, there were no significant differences in the maternal outcomes between cervical cerclage and vaginal progesterone groups, such as median gestational age at delivery (37.4 weeks vs. 37.3 weeks, $P = 0.346$) and proportion of delivery ≥37 weeks' gestation (55.9% vs. 60.9%, $P = 0.569$). There were also no significant differences in the neonatal outcomes between the cervical cerclage and vaginal progesterone groups including the median birth weight (2750 g vs. 2810 g, $P = 0.145$), perinatal mortality (5.9% vs. 6.5%, $P = 0.908$), and 1-min Apgar scores (8.8% vs. 8.7%, $P = 0.984$).

Conclusions: Cervical cerclage showed more benefits in the maternal and neonatal outcomes than vaginal progesterone therapy for women with an asymptomatic short cervix and prior PTB history, while cervical cerclage and vaginal progesterone therapies showed similar effectiveness for women with an asymptomatic short cervix but without a history of PTB.

Key words: Cervical Cerclage; Cervical Incompetence; Preterm Delivery; Vaginal Progesterone

Introduction

About 70% of neonatal death and complications are due to preterm birth (PTB). PTB is the leading cause of perinatal morbidity and mortality worldwide, and its prevention is an important health-care priority. Preterm parturition is one of the great obstetrical syndromes and it is caused by multiple etiologies. The challenge of the prediction and prevention of

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PTB has been difficult to address. The cervical incompetence is a well-known risk factor for PTB, which causes about 15% of habitual abortion in 16–28 weeks. The incidence of cervical incompetence is about 0.1–2.0%,[1-3] while there is no ideal optimum treatment recommended currently. Although controversial, the traditional mainstay in the management of cervical incompetence is the application of transvaginal cervical cerclage.[2,4-11] Otherwise, progesterone therapy and cervical pessary, which are noninvasive, may also be effective management options.[3,12-14] In this study, we aimed to evaluate the effectiveness and safety of cervical cerclage and vaginal progesterone in the treatment of cervical incompetence with/without PTB history.

Methods

Study design and participants

We performed a hospital-based, single-center, stratified (with and without PTB history), retrospective cohort study on all women who were diagnosed with cervical incompetence and treated with cervical cerclage or vaginal progesterone at Beijing Hospital (Beijing, China) from January 2010 to October 2015. The study was approved by the Institutional Ethics Committee of Beijing Hospital. Women were identified through review of the discharge diagnosis, ultrasound database management system, and the operative schedules. Once the women were identified, all hospital records were obtained from the time of admission for cerclage placement or the administration of vaginal progesterone to delivery. From these charts, the following data were abstracted: maternal demographic factors (including maternal age, self-reported gravidity, parity, and prior obstetric history), details of the treatments, current obstetric history, details of delivery, complications after the treatment, and neonatal demographic data (including Apgar scores and birth weight).

After data extraction, only women who met criteria were included in the final analysis. Inclusion criteria including: (1) age of 18 years or old; (2) singleton gestation; (3) gestation between 15^{+0} to 29^{+6} weeks, which was estimated based on a reliable date for the last menstrual period or by ultrasound at 22 weeks of gestation or before; (4) a sonographic short cervix (≤25 mm), which need to be reviewed by another ultrasonic physician for quality assurance; (5) without signs or symptoms of preterm labor; and (6) received either cervical cerclage or vaginal progesterone therapy. Exclusion criteria included: (1) acute cervical dilation with membranes visible; (2) current or recent progesterone treatment or failure operation within the prior 4 weeks; (3) chronic medical conditions that would interfere the treatment (including seizures, psychiatric disorders, and uncontrolled hypertension); (4) inadequate follow-up data; or (5) received both two therapies. Among the women involved in the study, women who had at least one PTB before 32 weeks (including abortion in the second trimester attributed to the cervical competence) were included to the PTB history cohort and other women were included in the non-PTB history cohort.

All women who received cervical cerclage were given McDonald cerclage under local anesthesia[15] which was performed by a specialist or a consultant gynecologist. Moreover, before commencing the procedure, vaginal swab was taken for bacterial/fungal/mycoplasma culture and test of antibiotics sensitivity, and active infections should be treated with antibiotics. All women who received vaginal progesterone therapy were asked to self-administer the QiNing 2 pills (each pill containing 100 mg progesterone; Zhejiang Aisheng Pharmaceutical Co., Ltd., Zhejiang, China) once daily at night. Cervical cerclage and vaginal progesterone therapies were stopped at 37 weeks of gestation, or the moment when the patients presented with progressing premature labor, such as preterm rupture of the membranes or infection uncontrollable, whichever occurred first. Patients who developed preterm labor during the study were treated according to the standard clinical practice, including admission to the hospital, bed rest, tocolytic therapy, and steroid administration, if clinically indicated.

The primary outcomes of interest were the differences in gestational age at delivery and the rate of premature delivery. Secondary outcomes of interest included cervical length at 2 weeks after the start of treatment, neonatal outcomes, complications, and route of delivery.

Statistical analysis

Data were analyzed using the statistical software package SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Univariate analyses were performed to characterize the distribution of the data. Data were expressed as mean ± standard deviation (SD) if normally distributed, and Student's *t*-test was used for statistical comparison. Nonnormally distributed data were expressed as median (range), and analysis was performed using Mann-Whitney-Wilcoxon test. Categorical variables were analyzed using Chi-square test or Fisher's exact test. A $P < 0.05$ was considered to be statistically significant.

Results

A total of 198 women with cervical incompetence met the criteria and were involved in the study. Among these 198 patients, 118 patients (59.6%) were included in PTB history cohort and 80 patients (40.4%) were included in non-PTB history cohort. Of the 118 women in PTB history cohort, two women received vaginal progesterone at first, and then changed to receive cervical cerclage later by their own demands, so they were excluded from the final analysis. Finally 116 women in PTB history cohort were included in the final analysis.

In the PTB history cohort, 101 (87.1%) women were treated with cervical cerclage and only 15 (12.9%) were treated with vaginal progesterone therapy. In the non-PTB history cohort, 34 (42.5%) women were treated with cervical cerclage and 46 women (57.5%) were treated with vaginal progesterone therapy. The baseline characteristics of 196 women with cervical incompetence in this study are shown in Table 1. A significantly higher proportion of women in the

Table 1: The baseline characteristics of all women with cervical incompetence in this study (n = 196)

Characteristics	PTB history cohort (n = 116)				Non-PTB history cohort (n = 80)			
	Cervical cerclage group (n = 101)	Vaginal progesterone group (n = 15)	Statistical values	P	Cervical cerclage group (n = 34)	Vaginal progesterone group (n = 46)	Statistical values	P
Age (years), mean ± SD	26.8 ± 6.8	29.1 ± 7.1	1.979*	0.052	26.1 ± 5.9	27.2 ± 8.3	1.662*	0.096
Gestational age at the treatment (weeks), mean ± SD	14.1 ± 6.3	16.1 ± 8.8	0.679†	0.572	20.1 ± 7.3	21.14 ± 6.8	0.679†	0.631
Cervical length (mm), mean ± SD	11.4 ± 9.8	10.1 ± 10.5	0.676*	0.587	11.6 ± 7.8	10.3 ± 9.5	0.677*	0.512
Gravidity, median (range)	3 (1–5)	2 (1–5)	0.353†	0.789	2 (1–5)	2 (1–5)	0.211†	0.986
Parity, median (range)	1 (1–2)	1 (1–2)	0.146†	1.000	0 (0–2)	0 (0–2)	0.132†	1.000
Reproductive history, n (%)			0.002‡	0.965			0.274‡	0.714
Nulliparous	–	–			18 (52.9)	28 (60.9)		
Primiparous	60 (59.4)	9 (60.0)			14 (41.2)	15 (32.6)		
Multiparous	41 (40.6)	6 (40.0)			2 (5.9)	3 (6.5)		
Prior PRB, n (%)			1.534‡	0.216				
28–32 weeks	37 (36.6)	8 (53.3)			–	–		
<28 weeks	64 (63.4)	7 (46.7)			–	–		
Maternal complications, n	10	4	3.429‡	0.083	5	6	0.045‡	0.832
Preeclampsia	3	0			0	1		
Gestational diabetes mellitus	5	2			1	2		
Thyroid hypofunction	2	1			2	2		
Anemia	0	1			2	1		

*t-test; †Mann-Whitney-Wilcoxon test; ‡Chi-square test. –: Not applicable; PTB: Preterm birth; SD: Standard deviation.

PTB history cohort underwent cervical cerclage, compared with the non-PTB history cohort (87.1% vs. 42.5%, χ^2 = 43.874, P = 0.000). No significant differences were noted in baseline characteristics between the two treatment groups in either PTB history cohort or non-PTB history cohort, including gestational age at the treatment, cervical length, prior obstetric history (including gravidity, parity, and prior PTBs), and maternal complications during pregnancy (all P > 0.05). It was noted that the age of the vaginal progesterone group seemed to be older in the PTB history cohort, but the difference was not statistically significant (P = 0.052).

Table 2 depicts cervical length after treatment, the pregnancy outcomes, and adverse events in the two treatment groups in the PTB history cohort. As anticipated, cervical cerclage group had a significantly longer cervical length at 2 weeks after the start of treatment (23.1 ± 4.6 mm vs. 12.4 ± 9.1 mm, P = 0.002), higher proportion of delivery ≥37 weeks' gestation (63.4% vs. 33.3%, P = 0.008), bigger median birth weight (2860 g vs. 2250 g, P = 0.031), and lower proportion of neonates whose 1-min Apgar scores <7 (5.9% vs. 33.3%, P = 0.005), compared with vaginal progesterone group. No significant difference was found in other outcome measures between the two treatment groups. There were four cases of neonatal death in the cervical cerclage group. Among these four cases, two cases were PTBs due to premature rupture of membranes and abortion in 25^{+4} weeks and 26^{+1} weeks, respectively, and then were given up by the parents; one preterm neonate (in 28^{+1} weeks) was due to neonatal respiratory distress syndrome (NRDS) and one (in 29^{+2} weeks) due to neonatal severe pneumonia. There were two cases of neonatal death in the vaginal progesterone group, including one PTB in 25^{+6} weeks and then given up by the parents and one preterm neonate (27^{+2} weeks) with NRDS. In terms of delivery type, the rates of cesarean section seemed to be higher in the PTB history cohort (60.4% in cervical cerclage group and 66.7% in vaginal progesterone group) than the average rate in our department (32.6%) at the same time, but they did not significantly differ between the two treatment groups. The indications of cesarean section were mainly due to patient's requirements and PTB.

Table 3 shows the maternal and neonatal outcomes in the two treatment groups in the non-PTB history cohort. As shown, there were no significant differences in the maternal outcomes between cervical cerclage and vaginal progesterone groups, such as median gestational age at delivery (37.4 weeks vs. 37.3 weeks, P = 0.346) and proportion of delivery ≥37 weeks' gestation (55.9% vs. 60.9%, P = 0.569). In terms of neonatal outcomes, there was no significant difference in the median birth weight (2750 g vs. 2810 g, P = 0.145), perinatal mortality (5.9% vs. 6.5%, P = 0.908), and 1-min Apgar scores (8.8% vs. 8.7%, P = 0.984) between cervical cerclage and vaginal progesterone groups. Among the two cases of neonatal death in the cervical cerclage group, one case was membrane rupture in 25^{+1} weeks during the operation and abortion happened 2 weeks later, and then the parents gave up the child; and another case was inevitable abortion 2 weeks after the operation (27 weeks of gestation) and the child died. Among three cases in the vaginal progesterone group, two cases were membrane rupture in 1–2 weeks after the administration (24^{+2} and 25^{+1} weeks of gestation) and the child died, the other case was that the child was delivered in 27^{+4} weeks of gestation due to intrauterine infection.

Table 2: Maternal and neonatal outcomes in the PTB history cohort

Items	Cervical cerclage group (n = 101)	Vaginal progesterone group (n = 15)	Statistical values	P
Duration of treatment (weeks), median (range)	19.4 (10.1–21.4)	13.3 (7.6–23.0)	3.413*	0.001
Cervical length at 2 weeks after the start of treatment (mm), mean ± SD	23.1 ± 4.6	12.4 ± 9.1	3.167†	0.002
Gestational age at delivery (weeks), median (range)	37.2 (25.6–39.0)	34.6 (25.9–39.1)	2.143*	0.033
Delivery ≥37 weeks' gestation, *n* (%)	64 (63.4)	5 (33.3)	7.789‡	0.008
PRB, *n* (%)				
34–36^{+6} weeks	27 (26.7)	6 (40.0)		
28–33^{+6} weeks	8 (7.9)	2 (13.3)		
<28 weeks	2 (2.0)	2 (13.3)		
Type of delivery, *n* (%)			0.216‡	0.642
Vaginal delivery	40 (39.6)	5 (33.3)		
Cesarean delivery	61 (60.4)	10 (66.7)		
Composite perinatal morbidity, *n* (%)§	9 (8.9)	3 (20.0)	1.717‡	0.190
Perinatal mortality, *n* (%)	4 (4.0)	2 (13.3)	2.319‡	0.172
Birth weight (g), median (range)	2860 (810–3300)	2250 (780–2950)	1.054†	0.031
Birth weight, *n* (%)			5.68‡	0.028
≥2500 g	77 (76.2)	7 (46.7)		
<2500 g	24 (23.8)	8 (53.3)		
1-min Apgar scores <7, *n* (%)	6 (5.9)	5 (33.3)	11.319‡	0.005
Admission to NICU, *n* (%)	9 (8.9)	3 (20.0)	1.717‡	0.190

*Mann-Whitney-Wilcoxon test; †*t*-test; ‡Chi-square test; §Occurrence of any of the following events: Respiratory distress syndrome, Grade III/IV intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, or bronchopulmonary dysplasia. PTB: Preterm birth; NICU: Neonatal Intensive Care Unit; SD: Standard deviation.

Table 3: Maternal and neonatal outcomes in non-PTB history cohort

Items	Cervical cerclage group (n = 34)	Vaginal progesterone group (n = 46)	Statistical values	P
Duration of treatment (weeks), median (range)	18.9 (10.0–20.2)	15.4 (8.2–22.1)	3.211*	0.052
Cervical length at 2 weeks after the start of treatment (mm), mean ± SD	23.5 ± 6.1	14.6 ± 7.7	3.016†	0.003
Gestational age at delivery (weeks), median (range)	37.4 (25–39)	37.3 (26–39)	1.012*	0.346
Delivery ≥37 weeks' gestation, *n* (%)	19 (55.9)	28 (60.9)	0.606‡	0.569
PRB, *n* (%)				
34–36^{+6} weeks	9 (26.5)	12 (26.1)		
28–33^{+6} weeks	4 (11.8)	4 (8.7)		
<28 weeks	2 (5.9)	2 (4.3)		
Type of delivery, *n* (%)			0.305‡	0.581
Vaginal delivery	24 (70.6)	35 (76.1)		
Cesarean delivery	10 (29.4)	11 (23.9)		
Composite perinatal morbidity, *n* (%)§	3 (8.8)	5 (10.9)	0.090‡	0.764
Perinatal mortality, *n* (%)	2 (5.9)	3 (6.5)	0.013‡	0.908
Birth weight (g), median (range)	2750 (790–3410)	2810 (830–3250)	1.436*	0.145
Birth weight, *n* (%)			0.063‡	0.801
≥2500 g	19 (55.9)	27 (58.7)		
<2500 g	15 (44.1)	19 (41.3)		
1-min Apgar scores <7, *n* (%)	3 (8.8)	4 (8.7)	0.000‡	0.984
Admission to NICU, *n* (%)	4 (11.8)	5 (10.9)	0.015‡	0.901

*Mann-Whitney-Wilcoxon test; †*t*-test; ‡Chi-square test; §Occurrence of any of the following events: respiratory distress syndrome, Grade III/IV intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, or bronchopulmonary dysplasia. PTB: Preterm birth; NICU: Neonatal Intensive Care Unit; SD: Standard deviation.

In terms of the safety of these two therapies, no serious adverse events were reported in PTB and non-PTB history cohorts. To compare the adverse events between the two treatment groups in both cohorts, the women who received vaginal progesterone had a significantly lower rate of complications related to the study treatment (18.0% [11/61]) than those who received cervical cerclage (27.4% [37/135], $\chi^2 = 4.852$, $P = 0.028$).

The complications frequently reported included vaginal bleeding, pruritus, discharge, candidiasis, and nausea. The overall rate of perioperative complications related to cervical cerclage placement was 8.9% (12/135), which included rupture of fetal membranes (4/135 [3.0%]), cervical laceration (2/135 [1.5%]), infection (5/135 [5.2%]), or complications from anesthesia at placement (1/135 [0.7%]).

Discussion

Our results suggested that cervical cerclage could prolong gestational weeks more effectively than vaginal progesterone for women who had at least one prior PTB and an asymptomatic shortened cervical length detected by ultrasound examination in the second trimester. Both the proportion of delivery ≥37 weeks' gestation (63.4%) and the proportion of birth weight ≥2500 g (76.2%) in cervical cerclage group were higher than those of vaginal progesterone group in the PTB history cohort, which were consistent with a previous literature.[16]

Several studies had proved that the use of either cervical cerclage or vaginal progesterone was effective in the prevention of PTB in patients with a cervical length ≤2.5 mm.[1-3] A meta-analysis[17] was performed to compare cervical cerclage and vaginal progesterone indirectly, and the result of this meta-analysis was similar to our study, which showed that no statistically significant differences were found between the two interventions in reducing PTB or adverse perinatal outcomes for the women with an asymptomatic shortened cervical length and without prior PTB. In our study, the rates of PTB (<37 weeks) in both cervical cerclage and vaginal progesterone groups (44.1% and 39.1%, respectively) in the women who had an asymptomatic shortened cervical length and without prior PTB were similar with the rates reported in the meta-analysis (42.0% and 45.3%, respectively). Although the meta-analysis did not have subgroup analysis for women with and without PTB history, the rate of PTB (<37 weeks) of cervical cerclage group in the PTB history cohort (36.6%) in this study was still less than the results in the meta-analysis, which further suggested the effectiveness of cervical cerclage.

Either cervical cerclage or vaginal progesterone group did not report serious adverse events. As we know, large doses of progesterone for a long time application may be associated with fetal abnormalities or tumor, although none occurred in our study. It attributed to either the relatively low daily dose of progesterone, or the small number of the progesterone cohort, or the short follow-up duration. Follow-up is still carried out to investigate the long-term adverse effects. It was found that the overall rate of complications related to the interventions in cervical cerclage and vaginal progesterone groups were 18.0% and 27.4%, respectively, which were similar with the results in other studies.[18,19] The cervical cerclage replacement may have more complications than the vaginal progesterone therapy, which need to be taken into account for the selection of the optimal treatment to prevent PTB in the women with cervical incompetence during the midtrimester.

Due to the retrospective nature of the study, there were some differences between the two treatment groups, which may have influenced the results. First, the selection of the administration of cervical cerclage or vaginal progesterone depended mainly on the clinician's decision and patient's preferences based on the maternal situation. Moreover, the clinicians and patients tended to choose cervical cerclage for women with PTB history, while there may be some differences in the maternal situation which may influence the outcomes of the two methods. Second, may be the cervical cerclage group be more often cared by maternal-fetal medicine physicians compared with the vaginal progesterone group, so they may report the complications more frequently. In addition, this study was conducted in just one hospital, so the representative of the sample was limited. Until now, no study had directly compared cervical cerclage and vaginal progesterone for the prevention of PTB in women with a sonographic short cervix during the midtrimester, the results of this study could provide basic information for the further large-scale research.

The limitations of the study were that a relatively small number of women with PTB history who received vaginal progesterone therapy might have biased the results against the use of vaginal progesterone. The possible reason for this situation was that "no surgery is equal to no treatment" in many Chinese people's idea. In addition, since the women had adverse pregnancy outcome before, especially those who had spontaneous abortion >12 weeks, they might have considered receiving cervical cerclage without delay as their best option.

In conclusion, this study indicated that cervical cerclage showed more benefits in the maternal and neonatal outcome for women with an asymptomatic short cervix and prior PTB history, while cervical cerclage and vaginal progesterone therapies showed similar effectiveness for women without a history of PTB. Both the interventions were safe in the short follow-up duration. Although the cervical cerclage replacement may bring a little more minor complications, the long-term adverse effects of vaginal progesterone therapy needed to be considered.

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Conflicts of interest

There are no conflicts of interest.

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