Original Article

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Effects of Maternal Cervical Incompetence on Morbidity and Mortality of Preterm Neonates with Birth weight Less than 2000g

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Abstract

Objective: This study aimed to determine the impact of maternal cervical incompetence (with or without McDonald cerclage) on mortality and morbidity of preterm infant with birth weight <2000g.

Methods: 581 neonates were eligible for this study, 79 with cervical incompetence and 502 without it (control). Incidences of neonatal respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), neonatal necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), periventricular leukomalacia (PVL), severe asphyxia, small for gestational age (SGA), early-onset sepsis (EOS), and mortality were compared between the two groups.

Findings: Mean gestational age was earlier in cervical incompetence group than in control (30.2±2.1 vs 30.7±1.9, *P*<0.05). Except lower frequency of SGA, there were no significant differences in the incidences of RDS, BPD, ROP, PVL, IVH, NEC, EOS, severe asphyxia and mortality between the two groups. Infants with no cerclage had a higher prevalence of RDS (21/66 vs 9/13, *P*<0.05) compared to cerclage group due to lower mean gestational age (30.68±2.1 vs 28.6±1.4, *P*<0.01) and birth weight (1519.5±274.6 vs 1205.8±204.4, *P*<0.001), and clinical neonatal outcomes of the elective cerclage were similar to emergency cerclage in cervical incompetence groups.

Conclusion: Maternal cervical incompetence was not associated with postnatal adverse neonatal outcomes. Lower mean gestational age was a major risk associated with higher prevalence of RDS in preterm neonates with no McDonald cerclage, and emergency cerclage did not predict poor clinical neonatal outcomes.

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Key Words: Uterine Cervical Incompetence; Neonate; Mortality; Morbidity; McDonald Cerclage

Introduction

Even though there have been continual advances in neonatal care and a decline in mortality of preterm infants in the past several decades, the incidence of severe long-term sequelae[1-3] such as chronic lung disease and neurodevelopmental disability in survivors remains high, particularly in newborns delivered at early gestational ages. It is an important public health issue as rates of preterm birth are rising in many countries. So, prevention and management of preterm birth continue to be a major challenge worldwide.

Cervical incompetence is a known risk factor for preterm birth[4-6] and is considered responsible for 5% of extremely preterm deliveries (<28 weeks)[7]. The cervix plays a fundamental role in supporting a pregnancy and cervices of women with cervical incompetence show pathological dilation and shortening, leading to miscarriage or

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preterm birth. Different management strategies have been tried to prolong pregnancy and prevent preterm birth, including cervical cerclage. While some studies support this technique[4-6,8], others have failed to demonstrate benefits[9-11]. Infection and ensuing chorioamnionitis, bleeding and ruptured membranes are the most concerning complications associated with cervical cerclage[12-15].

Of these complications associated with cervical incompetence, the impact of intrauterine infection on neonates is a major concern of neonatologists. When intrauterine infection occurs, the neonate is at significant risk for respiratory distress syndrome (RDS), retinopathy of prematurity (ROP), neonatal necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), inter-ventricular hemorrhage (IVH), periventricular leukomalacia (PVL), early-onset sepsis (EOS) and even mortality[16-19].

However, whether these complications caused by cervical cerclage and cervical incompetence itself could be associated with adverse neonatal outcomes remains unknown based on very little information. The objective of the present study was to analyze whether maternal cervical incompetence with or without cerclage was associated with postnatal morbidity and mortality in preterm neonates with birth weight <2000g, this information may help their mothers make an informed decision about whether to undergo cervical cerclage procedure from neonatologist's perspective.

Subjects and Methods

The study was approved by Research Ethics Committee in Beijing Obstetrics and Gynecology Hospital, Capital Medical University (Beijing, China). Written informed consent was obtained from patients or their relatives.

We performed a retrospective cohort study reviewing all preterm neonates with birth weight less than 2000g that were admitted to the neonatal intensive care unit or neonatal department of Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China between January 1, 2009 and December 31, 2013. The preterm births eligible for this study were divided into two groups: neonates born to mothers with cervical incompetence and those born to mothers without cervical incompetence. Twins, multiple births, neonates with chromosome abnormalities and/or congenital malformations, and those who died in the delivery room despite adequate resuscitation, were excluded.

Cervical incompetence was defined as painless dilatation and effacement of the cervix in the second trimester of pregnancy, resulting in situations of a miscarriage or a preterm birth in the absence of labor, or had sonographic evidence of cervical shortening (cervical length <2.5cm measured by transvaginal ultrasound) or funneling. Some women diagnosed cervical incompetence had McDonald type cerclage. Cervical cerclage either elective (when the clinical history suggests risk of mid-trimester loss) or emergency (when there is evidence of a short cervix <25 mm or cervical shortening on ultrasound) was performed based on the attending obstetrician's judgment.

Gestational age was based on mother's last menstrual period (LMP) or verified by early ultrasound examination if the mother's menstrual period was irregular or LMP was unknown. As co-morbidities, RDS, EOS, BPD, ROP, PVL, IVH (above grade 3), NEC, severe asphyxia small for gestational age (SGA), and mortality of premature neonates were analyzed in the experimental and control groups.

Diagnosis of RDS was based on clinical symptoms and chest X-ray findings. NEC was defined as Bell's stage II or greater[20] and BPD was defined as oxygen dependence at 36 weeks postmenstrual age. We categorized infants as SGA if their birth weights were less than the 10th percentile for their gestational age. ROP was diagnosed by ophthalmologists according to the criteria of the International Classification of Retinopathy of Prematurity[21]. EOS is defined as the presence of clinical signs of systemic inflammation and blood culture-proven bacterial infection of the newborn occurring in the first 3 days of life. Diagnosis of IVH was based on cranial sonograms which were performed routinely, daily in the first week of life and weekly thereafter until hospital discharge, or more frequently if clinically indicated for all preterm newborns, the

definitionof IVH was based on the Papil grading system[22]. PVL was diagnosed on serial cranial ultrasound examinations done by a pediatric neurologist. Severe asphyxia was defined as Apgar score <3 at 1 minute or <7 at 5 minutes[23-25].

Gestational diabetes mellitus (GDM) was diagnosed based on a 75-g 2-hour oral glucose tolerance test (OGTT) at pregnancy 24–28 weeks according to WHO diagnostic criteria[26], GDM refers to various degrees of abnormal glucose tolerance occurring or found for the first time during pregnancy. Maternal hypertension was defined as any condition including preeclampsia, eclampsia, and chronic hypertension. Clinical chorioamnionitis was defined[27] by >2 of 6 signs: 1) fever >38°C, 2) hysteralgia, 3) fetal tachydardia (>160 beats/minute), 4) maternal tachydardia (>100/minute), 5) foul-smelling amniotic fluid, 6) increased WBC count (≥12000/mm3).

Prolonged rupture of membrans (PROM) was defined as rupture of membranes lasting more than 18 hours before labor[28].

All numerical values are expressed as mean±SD. Continuous data were compared by Student's *t*-test, and comparisons between proportions were assessed by either the chi-square test or Fisher's exact test. A *P*-value <0.05 was considered statistically significant. SPSS v.19.0 was used for all statistical calculations.

Findings

A total of 581 neonates with birth weight less than 2000g were included in the study. Of these, there were 79 cases born to mothers with cervical incompetence and 502 to mothers without cervical incompetence. The mean gestational age among the preterm babies born to mothers with cervical incompetence was lower than control group. Infants with maternal cervical incompetence had a higher incidence of PROM, maternal antibiotic therapy and clinical chorioamnionitis than in control group, while incidence of maternal hypertension was higher in the control group. In patient characteristics such as birth weight, frequency of female, vaginal delivery, maternal diabetes mellitus, and antenatal steroid therapy, there was no difference between the two groups. Characteristics of the study population sample are presented in Table 1.

We compared morbidity and mortality of preterm neonates (Table 2) and found no significant differences in the incidences of RDS, ROP, BPD, PVL, IVH, NEC, severe asphyxia, EOS, and mortality between cervical incompetence and control groups. A lower incidence of SGA was detected in preterm infants in the cervical incompetence group than in control group.

In 13 out of 79 mothers, McDonald cerclage was not performed in the cervical incompetence group. The effects of McDonald cerclage on postnatal morbidity and mortality of preterm neonates are shown in Table 3. There were no significant differences in the incidences of ROP, BPD, PVL, IVH, NEC, severe asphyxia, EOS, SGA, and mortality between the two groups. Infants with no cerclage had a higher prevalence of RDS compared to cerclage group.

Emergency cerclage was performed in 8 out of 66 patients in the cervical incompetence group. Table 4 shows a comparison of postnatal

Table 1: Demographics and clinical characteristics of preterm neonates between cervical incompetence (case) and control groups

Demographics and clinical characteristics	Case group n=79	Control group n= 502	*P*. value
Gestational age, weeks (mean±SD)	30.2 (2.1)	30.7 (1.9)	0.03
Birth weight, g (mean±SD)	1467.9 (288.1)	1507.0 (270.4)	0.2
Premature rupture of membranes	45/79	172 (37.3%)	<0.001
Female	42/79	222 (44.2%)	0.1
Vaginal delivery	55/79	304 (60.6%)	0.7
Gestational diabetes mellitus	2/79	41 (8.2%)	0.1
Maternal antibiotic therapy	66/79	178 (35.7%)	<0.001
Antenatal steroid therapy	52/79	302 (60.2%)	0.338
Maternal hypertension	3/79	122 (21.5%)	<0.001
Clinical chorioamnionitis	6/79	15 (3.0%)	0.04

Table 2: Postnatal morbidities of preterm neonates in the CI with cerclage (case) and control groups

Postnatal clinical data	CI group n=79	Control group n=502	*P.* value
Neonatal respiratory distress syndrome	30/79	152 (30.3%)	0.2
Retinopathy of preterm neonates	5/79	17 (3.4%)	0.2
Bronchopulmonary dysplasia	16/79	63 (12.5%)	0.06
Periventricular leukomalacia	2/79	8 (1.6%)	0.6
Intracranial hemorrhage (above grade 3)	2/79	5 (1.0%)	0.2
Neonatal necrotizing enterocolitis	2/79	3 (0.6%)	0.1
Severe asphyxia	2/79	19 (4.9%)	0.4
Small for gestational age	1/79	45 (9.0%)	0.01
Early-onset sepsis	12/79	43 (8.6%)	0.06
Mortality	4/79	10 (2.0%)	0.1

CI: cervical incompetence

morbidity and mortality of preterm neonates between elective-cerclage and emergency cerclage in cervical incompetence group. Incidence of RDS, ROP, BPD, PVL, IVH, NEC, severe asphyxia, EOS, SGA, and mortality were not different between elective cerclage and emergency cerclage groups.

Table 3: Postnatal morbidities between the cerclage and no cerclage in cervical incompetence groups

Postnatal clinical data	With cerclage n=66	No cerclage n=13	*P.* value
Neonatal respiratory distress syndrome	21/66	9/13	0.02
Retinopathy of preterm neonates	3/66	2/13	0.2
Bronchopulmonary dysplasia	11/66	5/13	0.07
Periventricular leukomalacia	1/66	1/13	0.3
Intracranial hemorrhage (above grade 3)	1/66	1/13	0.3
Neonatal necrotizing enterocolitis	1/66	1/13	0.3
Severe asphyxia	2/66	0	1.0
Early-onset sepsis	9/66	3/13	0.4
Small for gestational age	1/66	0	1.0
Mortality	3/66	1/13	0.5

To analyze factors associated with frequency of RDS, clinical characteristics of the cerclage and no cerclage in cervical incompetence group are presented in Table 5. The mean weeks of gestation and mean birth weight were significantly lower in no cerclage group. There was no significant difference in the incidence of antenatal steroid therapy between the two groups.

Table 4: Postnatal morbidities of preterm neonates in the CI with elective cerclage and emergency cerclage groups

Postnatal clinical data	Elective cerclage n=58	Emergency cerclage n=8	*P*-value
Neonatal respiratory distress syndrome	17/58	4/8	0.2
Retinopathy of preterm neonates	2/58	1/8	0.3
Bronchopulmonary dysplasia	8/58	3/8	0.1
Periventricular leukomalacia	1/58	0	1.0
Intracranial hemorrhage (above grade 3)	1/58	0	1.0
Neonatal necrotizing enterocolitis	1/58	0	1.0
Severe asphyxia	1/58	1/8	0.2
Early-onset sepsis	6/58	3/8	0.07
Small for gestational age	1/58	0	1.0
Mortality	2/58	1/8	0.3

CI: cervical incompetence

Table 5: Clinical characteristics of the cerclage and no cerclage in cervical incompetence group

Clinical characteristic	CI group n=66	Without cerclage n= 13	*P*-value
Gestational age, weeks (mean±SD)	30.68 (2.1)	28.6 (1.4)	0.001
Birth weight, g (mean±SD)	1519.5 (274.6)	1205.8 (204.4)	<0.001
Antenatal steroid therapy	46/66	6/13	0.1

CI: cervical incompetence

Discussion

The cervix plays a fundamental role in supporting a pregnancy. It is increasingly being accepted that the cervix plays more than just a mechanical role, it also acts as a barrier to prevent ascending infection from the lower genital tract. Cervical incompetence and infection have long been regarded as major causes of preterm birth.

Meanwhile little is known about the mortality and morbidity of preterm neonates born to mothers with cervical incompetence. Was the frequency of postnatal sequelae in preterm neonates born to mothers with cervical incompetence higher than in those born to mothers without cervical incompetence? In this study, we found that, except for lower frequency of SGA in cervical incompetence group, there were no statistical differences in the incidences of RDS, BPD, severe IVH, NEC, EOS, ROP, PVL, severe asphyxia and mortality between the cervical incompetence and control groups. Our results agree with those of Tae-Jung Sung[29] and disagree with the findings of Mitani et al[30] which indicated that cervical incompetence was a significant factor related to the occurrence of neonatal death and abnormal cerebral ultrasound scans. Increasing evidence suggeststhat pathologically early cervical ripening associated with cervical incompetence was related with intrauterine infection or inflammation[31], so we speculated that there might be higher frequency of EOS of preterm neonates in cervical incompetence group, but it did not occur as expected. We examined the clinical characteristics of neonates and found that frequency of maternal antibiotic therapy was very high in cervical incompetence group. Whether intrapartum antibiotic prophylaxis (IAP) provided for women with cervical incompetence could alter the outcome of pregnancy and the newborn infant, is currently uncertain. Nonetheless, Lee et al[32] have reported that intra amniotic inflammation was present in approximately 80% of patients with acute cervical incompetence and suggested that parenteral antibiotic treatment may sometimes reduce the intensity of the intra amniotic inflammatory response, prolonging the time interval to delivery and improving neonatal outcome. Natale et al[31] believed that antepartum group B streptococcal (GBS) antibiotic prophylaxis may reasonably be useful in the subset of patients with CI/bulging membranes. So, higher frequency of maternal antibiotic therapy in our study may explain why incidence of EOS of preterm neonates in cervical incompetence was not higher than in control group. We also found that frequency of maternal hypertension was lower in cervical incompetence group which may result in lower incidence of SGA in this group.

Cervical cerclage is an intervention that is widely used to prevent miscarriage or delivery in the second trimester of pregnancy. It was described by Shirodkar in 1955 and then by McDonald two years later. Why the procedure is still a matter of controversy in obstetrics at present? One possibility is the complications caused by the operation[9-11]. These include infection and ensuing chorioamnionitis, ruptured membranes, bleeding, miscarriage, and cervical laceration requiring repair, etc. The effect of the procedure of cervical cerclage on the mortality and morbidity of newborns is a major concern for neonatologists. In this study, infants with no cerclage had a higher prevalence of RDS compared to cerclage group; incidence of neonatal BPD, PVL, severe IVH, NEC, EOS, ROP, SGA, severe asphyxia and mortality were not affected by cerclage status. Our results disagree with those of Tae-Jung Sung[29] that found no significant difference in the incidences of RDS in cerclage and no cerclage groups. Since many risk factors are associated with frequency of RDS, we analyzed clinical characteristics of preterm neonates in cerclage and no cerclage groups, and found that the neonates from mothers with no cerclage status were much smaller and younger. This result

suggests that lower gestational age and birth weight may result in higher incidence of RDS in neonates with no cerclage, the lower the gestational age, the higher the risk of RDS.

Cervical cerclage may be performed prophylactically in the first trimester (elective cerclage) when the clinical history suggests risk of mid-trimester loss or as emergency at mid-trimester when there is evidence of a short cervix or cervical shortening on ultrasound. It was reported[33] that emergency cerclage carried the highest complication rate and the outcome of these pregnancies was usually poor, so placement of emergency cerclage at mid-trimester was controversial. Andrea Liddiard et al[34] recently reported that there was little difference in the gestation at delivery (35 vs 33 weeks), live birth rate (93% vs 92%) and mean birth weight between the elective and emergency cerclage groups. Clinical neonatal morbidity with emergency cerclage based on limited information is not well known at present. Hence, we compared the neonatal outcomes between the elective and emergency cerclage status in this study. We found that there was no statistical difference between the two groups in the incidences of RDS, BPD, severe IVH, NEC, EOS, ROP, PVL, SGA, severe asphyxia, and mortality of neonates. This result suggests that the neonatal outcomes were not affected by emergency cerclage status in this study.

It was reported that cervical incompetence occurs in 1% of the obstetric population and up to 8% of patients with recurrent midtrimester losses[35]. Most patients and clinicians when faced with risk factors for preterm delivery seem to prefer intervention over no intervention. Cervical cerclage remains a common procedure that is offered to women at moderate to high risk. Both patients and clinicians worry about the safety of this procedure for fetus or newborns, which maybe result in no improvement in obstetrical outcomes or adverse neonatal outcomes.

Overall, neonatal outcomes in the cervical incompetence group in our study are somewhat encouraging, but there are some limitations to this study. Since pathology of placentas was not screened in all neonatal mothers enrolled in this study, we could not collect enough data to analyze the incidence of histopathological chorio-amnionitis between cervical incompetence and control groups. Another limitations of our study were the small sample size and retrospective time frame, only 8 samples were enrolled in the emergency cerclage group and 13 samples in no cerclage group, which were still not representative of such clinical features in these preterm infants. Thus, our results need to be verified by a larger population study.

Conclusion

The results of this study provide evidence that maternal cervical incompetence, regardless of cerclage status, was not associated with postnatal adverse neonatal outcomes. These findings can be beneficial to clinicians in the counseling and clinical management of these challenging patients.

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Authors' Contribution

Concept/Design: W.Hua, Z. Wei, F. Ling
Acquisition of Data and Data Analysis: F. Ling, Y. Song, M. Jian-Rong, W. Ping
Manuscript Preparation: W. Hua
Critical Revision of the Manuscript: W. Hua, Z. Wei
All authors approved final version of the manuscript.

Conflict of Interest: None

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