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## Original Article

## Preliminary preventive protocol from first trimester of pregnancy to reduce preterm birth rate for dichorionic–diamniotic twins



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## ABSTRACT

**Objective:** The preterm birth rate of twins is reportedly higher than that of single pregnancies. We performed preliminary preventive interventions at our center focused on evaluating the risk of each case before 14 weeks of gestation to reduce the spontaneous preterm birth rate.**Materials and methods:** The participants included 184 dichorionic–diamniotic twins delivered at our center during the 8 years from 2006. We evaluated each patient regarding high-risk status (at least 1 additional factor as follows: threatened abortion, history of chorioamnionitis, cervicitis, and bacterial vaginosis), based on available evidence; patients deemed high risk gave their informed consent and underwent treatment for cervicitis and cerclage if indicated. We divided the patients into two groups depending on whether the management was initiated before (Group A) or after (Group B) 14 weeks. We further divided Group A into three: Group 1 underwent treatment for cervicitis, Group 2 underwent cervical cerclage in addition to treatment for cervicitis, and Group 3 did not undergo preventive treatment. We retrospectively compared the preterm birth rates of the two groups, and we also compared them between the higher-risk group (Group 1 + 2) and the no additional risk group (Group 3) in Group A. **Results:** The spontaneous preterm birth rate < 36 weeks was significantly lower in Group A (4/90; 4.4%) than in Group B (18/94; 19.1%) ( $p = 0.001$ ). However, there were no significant differences between Group 1 + 2 and Group 3 (2/42 vs. 2/46). Focusing on the spontaneous preterm birth rate < 34 weeks, Group A had a lower rate than Group B (2/90; 2.2% vs. 13/94; 13.8%,  $p = 0.0012$ ).**Conclusion:** Even though this was a preliminary study, the results are promising, and we propose custom-made management for dichorionic–diamniotic twins: (1) earlier management from before 14 weeks; (2) high-risk selection for cervicitis and a short cervix; and (3) intervention with anti-inflammatory agents and cerclage if indicated.© 2017 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

The preterm birth rate of twins is reportedly higher than that of single pregnancies [1]. However, almost no reports on spontaneous preterm birth rates exist. Moreover, various risk factors for preterm birth have been reported [2]. To establish a simple management protocol is difficult because of these multifactorial problems, and because cerclage for twins remains controversial [3,4].

We therefore performed preliminary but fixed interventions at our center to prevent preterm births. When considering our

protocol, we especially focused on earlier prevention and a simple protocol, but we covered inflammation and cervical incompetence.

First, we focused not on monochorionic twins but on dichorionic–diamniotic (DD) twins to eliminate the bias associated with Twin-to-twin transfusion syndrome (TTTS) and selective intra-uterine growth retardation etc. Here, we report a retrospective case–control study of prevention of preterm deliveries of DD twins.

## Materials and methods

This was a retrospective case–control cohort study. The sample included 184 DD twins delivered at our center from March 2005 to August 2013; they comprised all of the DD twins delivered at our center during this period. We evaluated the risk factors including threatened abortion [5,6], history of chorioamnionitis (CAM) [7],

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cervicitis [8,9], and bacterial vaginosis [10] during the first trimester (before 14 weeks of gestation). Specifically, we diagnosed repeated vaginal bleeding and/or abdominal pain as signs of threatened abortion, and checked whether there was a past history of CAM. When >100 leukocytes were observed per high-power field in a smear of cervical mucus, this was considered cervicitis. When *Lactobacillus* was not detected on cultures of vaginal secretions, this was considered bacterial vaginosis. Twin pregnancy in itself is a risk factor for preterm birth [11]. Those patients in whom one or more risk factors were observed and who gave their informed consent underwent treatment for cervicitis in accordance with the protocol of our center. The protocol period was 2 weeks, and in addition to intravaginal washing during this period, the patients were given ulinastatin trypsin inhibitor vaginal suppositories [12] (500 U/d) for suppression of leukocyte infiltration and metronidazole vaginal suppositories (250 mg/d) [10]. During the first week, cefmetazole was also administered intravenously (2 g/d for 3 days), and during the second week azithromycin [13] (500 mg/d for 3 days) was administered orally. Preventive cerclage was performed if cervical shortening (<3 cm) and/or funneling was observed during that time, whether or not the patients had any risk factors (Figure 1).

In light of the fact that risk assessments were performed at <14 weeks of gestation, we divided the patients into two groups: Group A, in which management was initiated before 14 weeks of gestation; and Group B, in which management was initiated after 14 weeks of gestation. Then, the preterm birth rates of these two groups, in addition to a group referred to our center after 14 weeks of gestation as a control (their risk assessment for the 1<sup>st</sup> trimester was unknown because they received care at another facility), were compared.

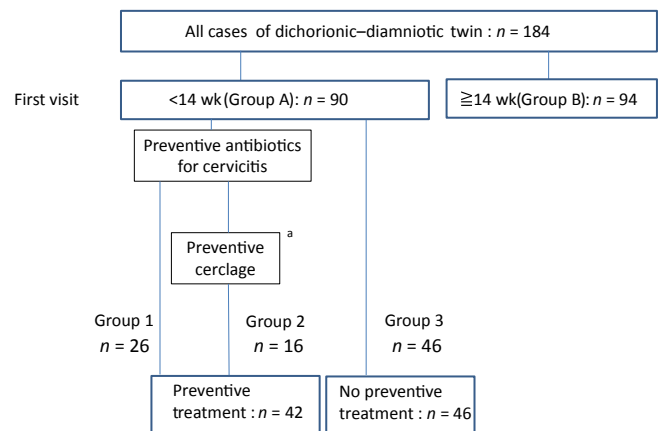
In addition, among the patients in whom management was initiated at our center before 14 weeks of gestation (Group A), those who were treated in accordance with the protocol were designated Group 1; those who underwent cervical cerclage in addition to treatment in accordance with the protocol were designated Group 2; and those who did not undergo preventive treatment were designated Group 3 (Groups 1 and 2 were considered higher risk

than Group 3). Spontaneous preterm birth excluded preterm births based on medical indications (e.g., pregnancy-induced hypertension, nonreassuring fetal status, placenta previa, and placental abruption).

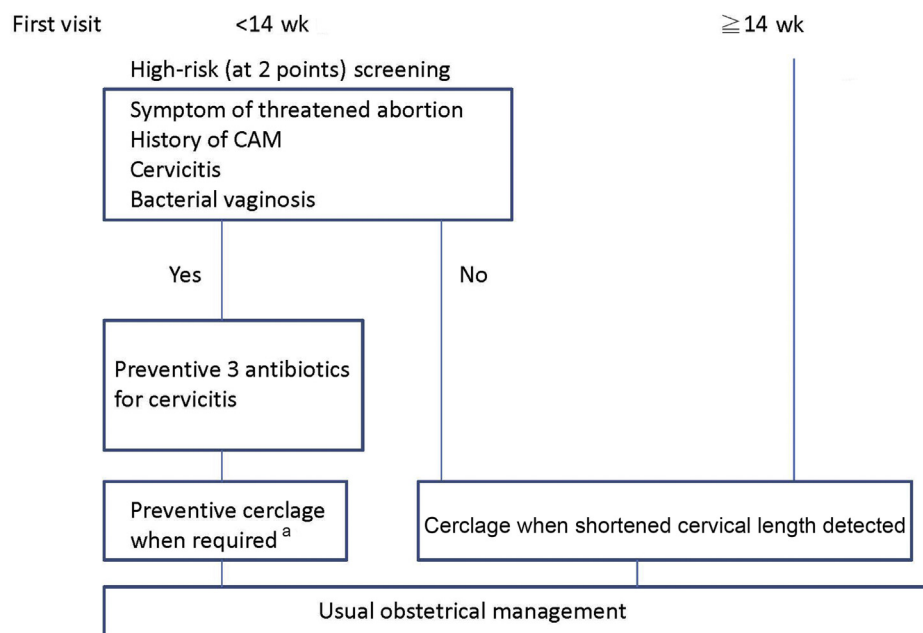
Statistical analysis was conducted using SPSS for Mac version 20 (IBM, Armonk, NY, USA). A *p* value < 0.05 was considered significant.

## Results

Of the 184 patients investigated, 90 were in Group A, in which management at this center was initiated before 14 weeks of gestation, and 94 were in Group B, in which management was initiated after 14 weeks of gestation (Figure 2). The number of patients who underwent cervical cerclage in each group was 18 in Group A and 16 in Group B (Table 1). All patients in Group A underwent cervical cerclage at our hospital, and in Group B, five patients underwent the procedure at our hospital, and 11 underwent



**Figure 2.** Grouping and the numbers of cases with our management protocol for dichorionic–diamniotic twin pregnancies. <sup>a</sup> Preventative cervical cerclage without antibiotics: *n* = 2.



**Figure 1.** A flow chart showing the grouping and management by risk factors in our department for dichorionic–diamniotic twin pregnancies. <sup>a</sup> Shortened cervical length <3 cm and/or funneling. CAM = chorioamnionitis.

the procedure at their previous physician's facility. A comparison of gestational age at delivery revealed that the spontaneous preterm birth rate was significantly lower in Group A than Group B for all three periods, before 34 weeks, 35 weeks, and 36 weeks of gestation (Table 2).

The numbers of patients were: Group 1, 26 patients; Group 2, 16 patients; and Group 3, 46 patients (Figure 2). In the group of patients in which management was initiated before 14 weeks of gestation at our center, no significant difference was seen in gestational age at delivery or the spontaneous preterm birth rate when compared based on the use of preventive treatment (Group 1 + 2 and Group 3; Tables 3 and 4). We successfully managed the patients in the higher-risk groups (e.g., twins with additional risk factors such as cervicitis, bleeding, and cervical length < 3 cm) without life-threatening earlier preterm delivery. In Group 3, we included one patient with symptoms of threatened abortion who did not undergo preventive treatment at her own request despite findings of cervicitis. This patient began spontaneous preterm labor at 31 weeks of gestation.

## Discussion

The rate of spontaneous preterm births before 36 weeks of gestation was significantly lower in Group A, in which management was initiated from an early stage of pregnancy, than Group B, in which management was initiated after 14 weeks of gestation at our center. Moreover, there was no significant difference in the rate of spontaneous preterm births according to the use of preventive treatment in the group in which management was initiated before 14 weeks of gestation. Identifying high-risk cases and performing medical intervention may make the spontaneous preterm birth rate of twins of high-risk cases equivalent to those at lower risk. Prediction of preterm birth in twins using biophysical and biochemical tests [14] and comparison of the preterm birth rate of twin pregnancies based on cervical length [15] was reported, but the majority of information about the first trimester was not included in that study. The risk of recurrence of preterm births was reported as 57% for twins after a previous preterm singleton birth [16], and the cervical length of the twins was summarized retrospectively [17].

**Table 1**  
Background of dichorionic–diamniotic twins.

Gestation of first visit <sup>a</sup>	< 14 wk (Group A)	≥ 14 wk (Group B)	Statistics
No. of cases	90	94	
Age (y)	31 ± 0.7	32 ± 5.7	NS
Multiparous, n (%)	43 (48)	40 (43)	
Cervical cerclage, n (%)	18 (20)	16 (20)	NS

NS = not significant.

<sup>a</sup> Time that pregnancy management was initiated at our center.

**Table 2**  
Outcome of spontaneous preterm birth rates divided by early management in our center from <14 weeks' gestation or late management after 14 weeks' gestation.

	First visit < 14 wk (Group A)	First visit ≥ 14 wk (Group B)	<i>p</i>
No. of cases	90	94	
Delivery < 34 wk	2 (2.2)	13 (13.8)	0.0012
Delivery < 35 wk	3 (3.3)	15 (16.0)	0.0003
Delivery < 36 wk	4 (4.4)	18 (19.1)	0.001

Data are presented as n (%).

Delivery: spontaneous preterm birth that excluded preterm births based on medical indications (e.g., pregnancy-induced hypertension, nonreassuring fetal status, placenta previa, placental abruption).

**Table 3**

Background of dichorionic–diamniotic twins gestation of first visit at <14 weeks to our center.

	Antibiotics (Group 1)	Antibiotics + cerclage (Group 2)	No treatment (Group 3)
No. of cases	26	16	46
Multiparous	11 (42)	6 (38)	25 (54)
Symptom of threatened abortion <sup>a</sup>	11 (42)	10 (63)	1 (2.2)
History of CAM	0	4 (25)	1 (2.2)
Cervicitis <sup>b</sup>	18 (69)	11 (69)	1 (2.2)
Bacterial vaginosis	12 (46)	3 (19)	0

Data are presented as n (%).

CAM = chorioamnionitis.

<sup>a</sup> Serial bleeding, subchorionic hematoma, lower abdominal pain.

<sup>b</sup> Greater than 100 leukocytes in high-power field by cervical cytology.

**Table 4**

Outcome of spontaneous preterm birth rate divided by preventative treatment among our early management group from <14 weeks' gestation.

	Treatment <i>n</i> (%) (Group 1 + 2; high risk)	No treatment <i>n</i> (%) (Group 3)	<i>p</i>
No. of cases	42	46	
Birth week (mean ± SD)	37.3 ± 5.8	37.5 ± 1.3	NS
Delivery < 34 wk	0 (0)	2 (4.3)	NS
Delivery < 35 wk	2 (4.8)	2 (4.3)	NS
Delivery < 36 wk	2 (4.8)	2 (4.3)	NS

Treatment: preventative antibiotics and/or cervical cerclage. Group 1: those who were treated in accordance with the protocol.<sup>a</sup> Group 2: those who underwent cervical cerclage in addition to treatment in accordance with the protocol.<sup>a</sup>

Group 3: those who did not undergo preventive treatment.

NS = not significant.

<sup>a</sup> Protocol: fixed medical interventions at our center to prevent preterm births.

We established a preliminary method of identifying high-risk cases among twins based on various studies (Figure 1) that was simple. When >100 leukocytes were observed per high-power field in a smear of cervical mucus, we considered that to be cervicitis. This standard was established by making reference to the report of Luo et al [18] in 2000, which found that interleukin-8 was involved in the increase of cervical granulocytes.

Some reports have stated that preterm births increased following cervical cerclage performed for cervical shortening in twin pregnancies [3]. However, cervical cerclage is not necessarily performed in all cases, and patients with short cervixes were carefully selected in our protocol. For example, we did not perform cerclage under inflammatory conditions before anti-inflammatory treatment. The controversies of management of preterm birth would understandably surface with such complicated criteria. For example, it is likely that merely performing a cerclage is not an adequate solution. Therefore, we hope to propose custom-made management for DD twins: (1) earlier management from before 14 weeks of gestation; (2) high-risk selection of cervicitis and short cervix; and (3) intervention with anti-inflammatory agents and cerclage if necessary. In addition, we also did not observe any serious adverse events using this preliminary protocol.

The literature contains few reports on the rate of spontaneous preterm births involving twins. The reported preterm birth rate for twins in the United States in 2008 was 58.8% for deliveries before 37 weeks of gestation, and 11.4% for deliveries before 32 weeks of gestation [19]. However, reports from Japan have calculated this rate from statistics based on the gestational age of twins and cited a 39.1% rate for deliveries before 37 weeks of gestation and 25.6% for deliveries before 36 weeks of gestation [1]. Twins are also often born prematurely for reasons different than those of a singleton

pregnancy; however, investigating the rate of spontaneous preterm births is important for the development of preventive measures. Moreover, there are no global guidelines regarding the management of twins for prevention of preterm birth. We hope to assist in the establishment of management guidelines for the prevention of preterm birth in twin pregnancies.

This study had some limitations in that this was not a randomized control trial. Our data are better than those in recent reports [20,21] using cervical pessary and vaginal progesterone, this study that was a non-randomized controlled trial might influence the result. Although our management approach seems effective for prevention in DD twins, a prospective study with a larger sample size and randomized control trial are needed for the next steps.

Compared with recent reports for preterm birth rate for twins before 34 weeks of gestation, 13.6% (80/590) with cervical pessary versus 12.9% (76/590) as control [20], and 18.5% (35/189) with vaginal progesterone after 18 weeks of gestation versus 14.6% (28/191) as control [21], we reported 2.2% (2/90) using custom-made intervention with high-risk selections from earlier periods before 14 weeks of gestation and cerclage and anti-inflammatory drugs if necessary. Since the both recent randomized control trials for twins showed no evidence to reduce preterm birth rate, our new protocol might be an effective and promising method even though it seems to be complicated.

In conclusion, we propose for consideration a custom-made management strategy for DD twins: (1) earlier management from before 14 weeks of gestation; (2) high-risk selection of cervicitis and short cervix; and (3) intervention with anti-inflammatory agents and cerclage if necessary. This protocol might be preliminary, but it holds promise for reducing the preterm delivery rate of twin pregnancies.

## Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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