Pessary Compared With Vaginal Progesterone for the Prevention of Preterm Birth in Women With Twin Pregnancies and Cervical Length Less Than 38 mm

A Randomized Controlled Trial

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OBJECTIVE: To compare the effectiveness of cervical pessary to vaginal progesterone for the prevention of preterm birth in women with twin pregnancies and short cervix.

METHODS: This randomized controlled trial was conducted at My Duc Hospital, Vietnam. Asymptomatic women with twin pregnancies and cervical length less than 38 mm were randomized to Arabin pessary or vaginal progesterone (400 mg once a day) group. The primary outcome was preterm birth at less than 34 weeks of gestation. Secondary outcomes were adverse maternal and perinatal complications. We planned a subgroup analysis according to quartile of cervical length. Analysis was conducted on an intention-to-treat basis. We estimated that the primary outcome would occur in 28.4% of women treated with progesterone. Thus a total sample size of 290 women divided equally into two groups was required to detect a 14% absolute risk difference in the primary outcome between the two groups (power 80%, alpha-error 5%, 10% loss to follow-up).

RESULTS: Between March 2016 and June 2017, we randomized 300 women, 150 women in each group. Preterm birth at less than 34 weeks of gestation occurred in 24 (16%) women in the pessary group and 33 (22%) women in the progesterone group (relative risk [RR] 0.73, 95% CI 0.46–1.18). The use of pessary significantly reduced the composite of poor perinatal outcomes (19% vs 27%; RR 0.70, 95% CI 0.43–0.93). In women with cervical length of 28 mm or less (25th percentile), pessary significantly reduced the preterm birth rate at less than 34 weeks of gestation from 46% (16/35) to 21% (10/47) (RR 0.47, 95% CI 0.24–0.90) and significantly improved the composite of poor perinatal outcomes.

CONCLUSION: Cervical pessary and 400 mg vaginal progesterone resulted in similar rates of preterm birth at less than 34 weeks of gestation in women with twin pregnancies and cervical length less than 38 mm.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, NCT02623881.

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Women with twin pregnancies are at increased risk for preterm birth. In the United States, data in 2013 showed that more than 50% of women with twin pregnancies gave birth before 37 weeks of gesta-

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tion and 11% before 32 weeks.[1] Corresponding figures in women with singleton pregnancies were 6–10% and 1%, respectively.[1] Short cervical length in the second trimester of pregnancy is well known to be an independent risk factor for preterm birth.[2,3] Therefore, women with twin pregnancies and a short cervix are at very high risk for preterm birth.[4,5]

Vaginal progesterone,[6,7] and cervical pessary[8–10] have been proposed as potential strategies to reduce preterm birth in this high risk population. A meta-analysis of randomized controlled trials (RCTs) suggested that progesterone potentially reduced preterm birth and neonatal complications in women with twin pregnancies and a short cervix.[7] Pessary does not reduce preterm birth in unselected women with twin pregnancies; however, in those with shortened cervix, the effectiveness of pessary is still controversial.[8–12]

In view of the significant effect of preterm birth and the promising, but not definitively established, effects of both pessary and progesterone, we conducted an RCT directly comparing the effectiveness of these two interventions in women with twin pregnancies and a short cervix.

METHODS

This single-center, open-label RCT was conducted at My Duc Hospital, Ho Chi Minh City, Vietnam, where approximately 1,000 women with twin pregnancies are seen each year. Written informed consent was obtained from all participants. The trial was approved by the institutional ethics committee of My Duc Hospital (IEC, 09/15/DD-BVMD), registered at ClinicalTrials.gov (NCT02623881) and reported according to Consolidated Standards of Reporting Trials (CONSORT) guidelines.[13]

Asymptomatic women with twin pregnancies at 16–22 weeks of gestation underwent cervical length measurement and digital examination as part of routine clinical care. For women who conceived after Assisted Reproductive Technology, gestational age was determined by the date of embryo transfer or intrauterine insemination. For patients who conceived naturally, gestational age was determined from the menstrual history and confirmed by the fetal crown-rump length of the larger twin at the first-trimester ultrasound examination. Cervical length was measured transvaginally by two ultrasonographers certificated by the Fetal Medicine Foundation. Prior to cervical length measurement, women were given a short brochure outlining risk factors and available preterm birth prevention methods.

Women with twin pregnancies and cervical length less than 38 mm were eligible for the study irrespective of chorionicity. Women with twin-to-twin transfusion syndrome, stillbirth, or major congenital abnormalities in one of the fetuses, history of cervical surgery, cervical cerclage, premature labor with or without ruptured membranes, severe vaginal discharge, acute vaginitis or cervicitis, or younger than 18 years were not eligible. The 38-mm cutoff in this trial was based on the result of a Dutch study that reported that in patients with cervical length less than the 25th percentile (less than 38 mm), pessary was associated with a reduced rate of preterm delivery and improved perinatal outcomes as compared with no intervention.[9]

Eligible participants were screened by midwives or obstetrician–gynecologists, then were provided a full patient information sheet and a consent form, then invited to a full discussion with investigators about the study. All eligible women were invited to participate in the study. After written informed consent, women were randomly assigned in a 1:1 ratio to receive a cervical pessary or vaginal progesterone. Randomization was done via telephone by two nurses who were not involved in the study, using a computer-generated randomized list, with a variable block size of two, four or eight. Blinding was not possible due to the nature of interventions. However, neonatologists assessing the neonates were unaware of treatment allocation. Apart from randomization, patients were followed up and treated according to local protocol. In both groups, a speculum inspection was performed to exclude prelabor rupture of membranes, acute vaginitis, and cervicitis.

In the pessary group, a senior clinician inserted a soft, flexible, silicone pessary, purchased from the manufacturer (Arabin), through the vagina, upward around the cervix within 1 week of randomization. The size of the pessary was determined at the time of speculum inspection.[14] The pessary was removed if prelabor rupture of membranes, active vaginal bleeding, other signs of preterm labor, or severe patient discomfort occurred.

In the progesterone group, 400 mg vaginal progesterone, purchased from the manufacturer (Cyclogest 400 mg), was applied once daily at bedtime, starting from the day of randomization. Participants were asked to record their drug application in a patient diary sheet for up to 140 days. Assessment for adverse events was first carried out at 14 days after randomization and at every visit after that. Cervical length measurement was not performed routinely after randomization. If the cervical length had shortened, further intervention, if any, was based on the clinician's decision after a discussion with the patient.

At every visit, participant compliance with progesterone therapy was documented by checking the patient diary and drug purchasing records from the

hospital pharmacy. The compliance rate was calculated by dividing the number of progesterone doses used since the previous visit by the number of progesterone doses that should have been used. Women were defined as being in compliance when the compliance rate was higher than 80%.

Interventions were stopped at 36 0/7 weeks of gestation or at delivery in both groups, whichever occurred sooner. In cases of preterm-threatened labor, patients were treated according to local protocol.

The primary outcome was preterm birth before 34 weeks of gestation for any indication. Secondary outcomes were fetal death before 24 weeks of gestation; stillbirth (defined as a fetus born with no signs of life at or after 28 weeks of gestation); delivery before 28 and 37 weeks of gestation; labor induction, delivery mode, live birth; tocolytic drugs or corticosteroids use; admission days for preterm labor; chorioamnionitis; maternal side effects (including vaginal discharge, fever, vaginal infection or pain, pessary repositioning and necrosis or rupture of the cervix); maternal morbidity (including thromboembolic complications, urinary tract infection treated with antibiotics, pneumonia, endometritis, hypertensive disorder, eclampsia, hemolysis, elevated liver enzymes, low platelet count syndrome, death); birth weight; birth weight less than 1,500 g and less than 2,500 g; congenital anomalies diagnosed after randomization; 5-minute Apgar score; 5-minute Apgar score less than 7; perinatal death, neonatal intensive care unit (NICU) admission; days of admission to the NICU; bronchopulmonary dysplasia; intraventricular hemorrhage; respiratory distress syndrome; necrotizing enterocolitis; and neonatal sepsis. Full definitions of these terms are provided in Appendix 1, available online at http://links.lww.com/AOG/B284.

Historically, the delivery rate before 34 weeks of gestation in women with twin pregnancies with cervical length less than 38 mm treated with 400 mg progesterone at My Duc Hospital was 28.4%. The null hypothesis was that there was no difference in delivery rate before 34 weeks of gestation between the two groups. Our original alternative hypothesis was that the absolute risk difference in delivery rate before 34 weeks of gestation between the two groups would be 10%, based on a clinically relevant reduction in risk. Therefore, a sample size of 520 women (power 80%, alpha-error 5%, loss to follow-up rate 10%) was required. After recruitment of the first 70 patients, it became clear that the number of women with cervical length less than 38 mm was lower than expected and the recruitment of that number of patients would take too long. Therefore, we re-calculated the sample size to detect a 14% absolute risk difference in the primary outcome between the two treatment groups (power 80%, alpha-error 5%). Allowing for a 10% loss to follow-up rate, the number of patients required was 290 (145 per group). This change was initiated by investigators and was approved by the institutional ethics committee after the recruitment of the first 98 women. Investigators were blinded to all outcome data until the recruitment came to an end.

Data analysis was performed on an intention-to-treat basis. Between-group differences in categorical variables were assessed using the Fisher exact test. For continuous variables, results were given as SD and between-group differences were assessed using Student *t* test. For dichotomous endpoints, relative risk (RR) and 95% CI values were calculated. Time to delivery was assessed using a Cox proportional hazard analysis and Kaplan-Meier estimates, where gestational age was the time scale, birth was the event, and results were compared using a log-rank test. Hazard ratio (HR) values were estimated using a Cox proportional hazards model, with a formal test of the proportional hazards assumption. For neonatal outcomes, we used cluster analysis, taking into account the dependency between the twins.[15]

We planned a prespecified subgroup analysis by quartile of cervical length. We tested for interaction between cervical length and treatment effect on preterm birth before 34 weeks of gestation and the composite of poor perinatal outcomes. A composite of poor perinatal

Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *Yes.*

What data in particular will be shared: *Data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices)*

What other documents will be available? *Study protocol will be available.*

When will data be available (start and end dates)? *Data will be available beginning 9 months and ending 36 months following article publication.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *On request from investigators whose proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for this purpose to achieve aims in the approved proposal. Proposals should be directed to* bsvinh.dq@myduchospital.vn. *To gain access, data requestors will need to sign a data access agreement. Data are available for 5 years at* https://www.project-redcap.org/.

outcomes, defined as fetal or neonatal death, bronchopulmonary dysplasia, intraventricular hemorrhage, respiratory distress syndrome, necrotizing enterocolitis or neonatal sepsis, was investigated in a post hoc analysis. *P*-values <.05 were considered statistically significant. The statistical software R, 2.15.1 (R Foundation for Statistical Computing) was used.

RESULTS

Between March 4, 2016, and June 3, 2017, we screened 1,113 women, of whom 444 (39.9%) had cervical length less than 38 mm (Fig. 1). The 300 women who fulfilled all criteria and consented were randomly assigned to receive a cervical pessary (n=150) or vaginal progesterone (n=150). Patient follow-up was completed on November 2, 2017.

Baseline characteristics were comparable between the two groups (Table 1). In the progesterone group, 144 of 149 (97%) were in compliance with therapy. After randomization, seven patients in the progesterone group had additional treatments due to short cervical length (six underwent cerclage and one underwent pessary insertion); one patient in the pessary group was cotreated with progesterone. Antibiotics for asymptomatic urinary tract infection were used for 14 patients in the pessary group and 12 patients in the progesterone group. Three women were not included in the final analysis due to loss to follow-up (Appendix 2, available online at http://links.lww.com/AOG/B284).

Preterm birth before 34 weeks of gestation occurred in 24 (16%) women in the pessary group compared with 33 (22%) women in the progesterone group (RR 0.73, 95% CI 0.46–1.18, *P*=.24) (Table 2). The cumulative percentage of patients who did not give birth before 34 weeks of gestation was not statistically significant between the two groups (HR 0.93, 95% CI 0.73–1.17, log rank test *P*=.53) (Fig. 2). The risk of preterm birth at less than 37 weeks of gestation was significantly lower in the pessary group (Table 2). Other pregnancy outcomes are presented in Appendix 3, available online at http://links.lww.com/AOG/B284.

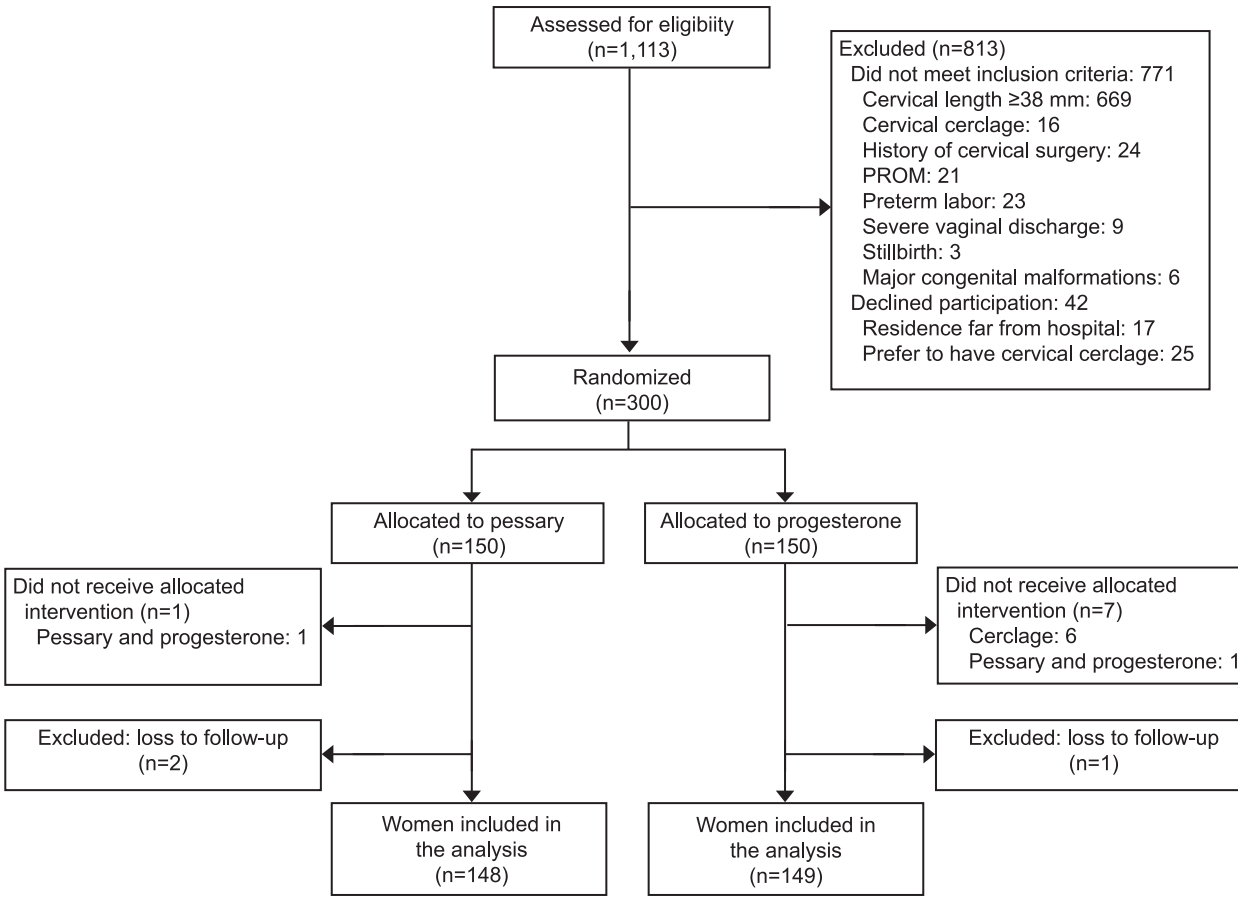

Fig. 1. Study flowchart. PROM, prelabor rupture of membranes.
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Table 1. Participant Characteristics at Baseline

Characteristic	Pessary (n=150)	Progesterone (n=150)
Age (y)	31.7±5.2	32.1±4.9
Highest completed education		
High school	51 (34)	44 (29.3)
University or higher	99 (66)	106 (70.7)
BMI (kg/m^2)	21.2±2.6	20.9±2.0
Nulliparous	125 (83)	135 (90)
Prior preterm birth	0 (0)	6 (4)
Conception		
Natural	5 (3)	2 (1)
Ovulation induction	6 (4)	5 (3)
In vitro fertilization	139 (93)	143 (95)
Fresh transfer	26 (19)	31 (22)
Frozen transfer	113 (81)	112 (78)
Dichorionic placentation	142 (95)	146 (97)
Uterine malformation	1 (1)	1 (1)
Gestational age at randomization (wk)	17.5±1.5	18.0±1.8
Cervical length at randomization (mm)	30.9±4.5	31.7±4.1
Cervical length range (mm)		
18–28	49 (33)	36 (24)
29–32	25 (17)	30 (20)
33–35	41 (27)	35 (23)
36 to less than 38	35 (23)	49 (33)
Funnelling	7 (5)	3 (2)

BMI, body mass index.
Data are mean±SD or n (%).

Mean birth weight did not differ significantly between the two groups. However, the use of pessary significantly reduced the rates of low birth weight (less than 2,500 g), admission to the NICU, and the number of neonates with composite of poor perinatal outcomes (Table 2). There were no cases of maternal death or serious vaginal trauma either during insertion or removal of the pessary.

The 25th, 50th, and 75th percentile cutoffs for cervical length were 28, 32, and 35 mm, respectively. The interaction between cervical length and treatment effect on preterm birth before 34 weeks of gestation was not statistically significant (P=.17), but there was a statistically significant interaction between cervical length and the rate of the composite of poor perinatal outcome endpoint (P=.026).

In women with cervical length of 28 mm or less, baseline characteristics were similar between the two groups (Appendix 4, available online at http://links.lww.com/AOG/B284). In this subgroup, the use of pessary was associated with a significant reduction in the risk of preterm birth before 34 weeks of gestation, preterm birth before 37 weeks of gestation, and the risk of poor perinatal outcomes (Table 3). The cumulative percentage of patients who did not give birth before 34 weeks of gestation was not significantly different between the two groups (HR 0.68, 95% CI 0.43 to 1.08, log rank test P=.10) (Fig. 2). In women with cervical length in the 25–50th percentile (29–32 mm), pessary significantly reduced the number of neonates with a composite of poor perinatal outcomes (RR 0. 38, 95% CI 0.10–0.91, P=.03) (Appendix 5, available online at http://links.lww.com/AOG/B284). In women with cervical length in the 50–75th percentile and 75th percentile or higher, preterm birth before 28, 34, or 37 weeks of gestation and other neonatal outcomes were comparable between the two groups (Appendixes 6, 7, 8, all available online at http://links.lww.com/AOG/B284).

DISCUSSION

Our data showed that pessary did not significantly reduce preterm birth before 34 weeks of gestation as compared with 400 mg progesterone in women with twin pregnancies and cervical length less than 38 mm. However, the study was powered to detect only a large risk reduction in the primary outcome–a 14% absolute rate reduction, that is, a 50% relative reduction, and the rate of some adverse secondary outcomes was significantly reduced with pessary.

Liem et al,[9] in a subgroup analysis of women with twin pregnancies and cervical length less than the 25th percentile (less than 38 mm), found that pessary was associated with a reduced risk of preterm birth before 28 and 32 weeks of gestation, but not before 37 weeks. This was associated with a significant reduction in perinatal mortality in the pessary group. In our study, we observed a reduction in neonatal morbidity but not in perinatal mortality. The discrepancy between the two studies might be due to the fact that we compared two interventions.

When interventions are introduced, they should be compared with either a standard treatment, a placebo, or no intervention. However, this has already been done in women with twin pregnancies for both pessary[8–11] and progesterone.[7] Although the effectiveness of these interventions in those with short cervix is debatable, available RCTs showed no negative effect of these treatments, for example, preterm birth or poor perinatal outcomes. Also, other ongoing studies are already comparing pessary to no treatment.[16] Thus, we chose to directly compare these two interventions, with the idea that the better of the two would also be better than no intervention or placebo and at

Table 2. Outcomes in the Overall Study Population

Outcome	Pessary (n=148)	Progesterone (n=149)	RR (95% CI)	*P*
Primary outcome				
PTB at less than 34 wk of gestation	24 (16)	33 (22)	0.73 (0.46–1.18)	.24
Secondary outcomes				
Gestational age at delivery (wk)	37 [35.5–37.5]	36.5 [34.3–37.5]	—	.50
PTB at less than 28 wk	9 (6)	7 (5)	1.29 (0.50–3.38)	.62
PTB at less than 37 wk	73 (49)	91 (61)	0.81 (0.66–0.99)	.05
Magnesium sulphate for neuroprotection	0 (0)	1 (1)	—	—
Antenatal corticosteroids	139 (94)	141 (95)	0.99 (0.94–1.05)	.81
Mode of delivery				.65
Vaginal	21 (14)	25 (17)		
Cesarean	127 (86)	124 (83)		.40
Elective	66 (45)	54 (36)		
Suspected fetal distress	14 (11)	17 (14)		
Nonprogressive labor	47 (37)	53 (43)		
Maternal side effects				
Vaginal discharge	104 (70)	36 (24)	2.91 (2.15–3.94)	<.001
Pruritis	4 (3)	8 (5)	0.50 (0.15–1.64)	.38
Vaginal infection	5 (3)	7 (5)	0.72 (0.23–2.21)	.77
Fever	0 (0)	0 (0)	—	—
Discomfort	25 (17)	16 (11)	1.57 (0.88–2.82)	.13
Pain	6 (4)	2 (1)	3.02 (0.62–14.72)	.17
Perinatal outcomes	n=296	n=298		
Birth weight (g)	2,315±612	2,236±592	-	.11
Very low birth weight (less than 1,500 g)	29 (10)	25 (8)	1.17 (0.68–2.08)	.57
Low birth weight (less than 2,500 g)	143 (48)	181 (61)	0.80 (0.44–0.84)	<.001
5-minute Apgar score	9 [8–9]	9 [8–9]	—	.66
5-minute Apgar score less than 7	11 (4)	8 (3)	1.38 (0.55–3.53)	.50
Congenital anomalies*	1 (0.3)	4 (1)	0.25 (0.03–2.24)	.37
Composite of poor perinatal outcomes†	55 (19)	79 (27)	0.70 (0.43–0.93)	.02
Stillbirth	14 (5)	13 (4)	1.08 (0.50–2.36)	.85
Neonatal death	7 (2)	4 (1)	1.76 (0.52–6.15)	.38
Bronchopulmonary dysplasia	0 (0)	0 (0)	—	—
Respiratory distress syndrome	32 (11)	51 (17)	0.63 (0.37–0.94)	.03
Intraventricular haemorrhage	3 (1)	2 (1)	1.51 (0.25–9.14)	.69
Necrotizing enterocolitis	8 (3)	18 (6)	0.45 (0.18–1.01)	.07
Neonatal sepsis	17 (6)	33 (11)	0.52 (0.27–0.90)	.03
Admission to NICU	39 (13)	66 (22)	0.59 (0.35–0.82)	.01

RR, relative risk; PTB, preterm birth; NICU, neonatal intensive care unit.
Data are no. of patients (%), median [range], or mean±SD unless otherwise specified.
* Congenital anomalies include Hirschsprung's disease, patent ductus arteriosus, cleft lip, and hypospadias.
† Post hoc analysis.

the same time satisfy any potential ethical or feasibility issues.

Except for a significantly higher number of women with vaginal discharge in the pessary group, rates of other side effects, including discomfort and pain, were similar between the two groups. These findings are consistent with other studies.[8–10] The safety of any interventions on neonates is also of particular concern. There is increasing data showing that progesterone has no negative effects on the neurodevelopmental and health outcomes of neonates.[17–19] A recent study also showed that pessary has no adverse long term neurodevelopmental effects in children at 3 years corrected age.[20]

As an exploratory analysis, we compared the effectiveness of both treatments in a prespecified subgroup according to the cervical length percentile. In women with cervical length in the 25–50th percentile, pessary might be more effective than progesterone. This effect is more profound in women with cervical length below the 25th percentile. A similar dose–response effect was also seen in the study of Liem et al.[9] These findings should be confirmed in other trials.

Strengths of our study include its randomized design, high compliance rate, a low loss to follow-up rate and a limited number of well-trained staff involved in cervical length measurement and pessary

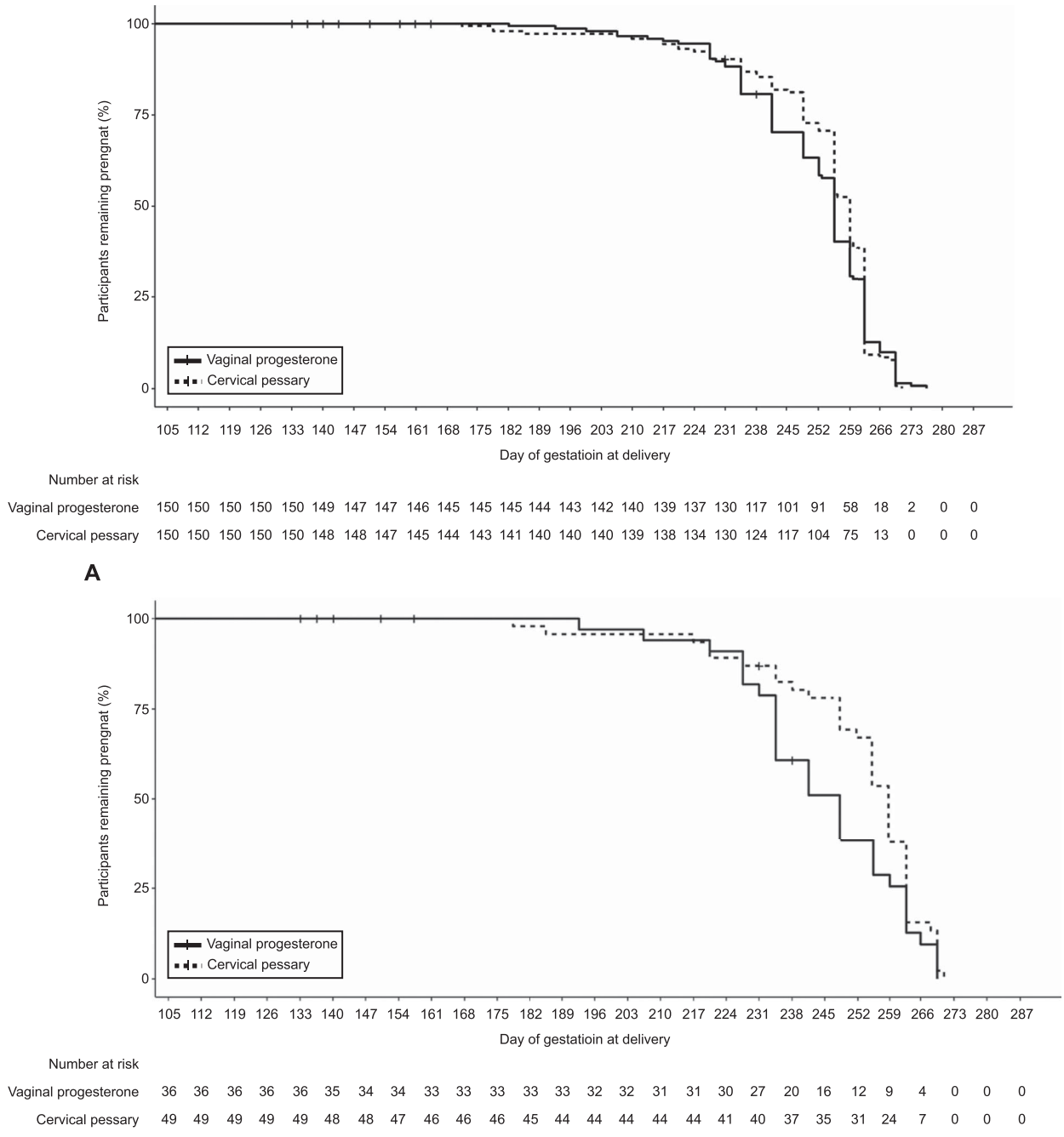

Fig. 2. Kaplan-Meier curves showing the proportion of continued pregnancies in all women (**A**) and women with cervical length less than the 25th percentile (28 mm or less) (**B**).

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placement. Moreover, the dose of 400 mg progesterone once daily could prevent potential concerns that our progesterone dose was too low for women with twin pregnancies. There are also some limitations that need to be taken into account. First, the study was conducted at a single center in Asia, and most included pregnancies that occurred after Assisted Reproductive Technology. Moreover, most patients in the study were nulliparous, highly educated, with low body mass index, and, on average, 32 years old, which might compromise the external validity of our study. Second, the study had an unblinded design due

Table 3. Outcomes in Women With Cervical Length 28 mm or Less (Below the 25th Percentile)

Outcomes	Pessary (n=47)	Progesterone (n=35)	RR (95% CI)	*P*
Secondary outcomes				
Gestational age at delivery (wk)	37 [35–37.5]	34.5 [32.8–36.8]	—	.09
PTB before 28 wk	4 (9)	4 (11)	0.74 (0.2–2.77)	.72
PTB before 34 wk	10 (21)	16 (46)	0.47 (0.24–0.90)	.03
PTB before 37 wk	23 (49)	26 (74)	0.66 (0.46–0.94)	.02
Mode of delivery				.99
Vaginal	7 (15)	6 (17)		
Cesarean	40 (85)	29 (84)		.53
Elective	22 (47)	12 (34)		
Suspected fetal distress	3 (6)	3 (9)		
Nonprogressive labor	15 (32)	14 (40)		
Perinatal outcomes	n=94	n=70		
Birth weight (g)	2,232±645	1,958 ±763		.01
Very low birth weight (less than 1,500 g)	12 (13)	12 (17)	0.74 (0.30–1.68)	.51
Low birth weight (less than 2,500 g)	50 (53)	51 (73)	0.73 (0.22–0.82)	.02
5-minute Apgar score	9 [8–9]	8 [7–9]	—	.12
5-minute Apgar score less than 7	6 (6)	1 (1)	4.47 (0.55–40.0)	.24
Congenital anomalies*	0 (0)	1 (1)	—	—
Composite of poor perinatal outcomes†	18 (19)	35 (50)	0.38 (0.12–0.47)	<.001
Stillbirth	4 (4)	7 (10)	0.43 (0.11–1.42)	.21
Neonatal death	3 (3)	0 (0)	—	—
Bronchopulmonary dysplasia	0 (0)	0 (0)	—	—
Respiratory distress syndrome	12 (13)	21 (30)	0.43 (0.15–0.75)	.01
Intraventricular haemorrhage	3 (3)	1 (1)	2.23 (0.23–22.34)	.64
Necrotizing enterocolitis	4 (4)	7 (10)	0.43 (0.11–1.42)	.21
Neonatal sepsis	6 (6)	15 (21)	0.30 (0.09–0.68)	.01
Admission to NICU	14 (15)	28 (40)	0.37 (0.12–0.55)	<.001

RR, relative risk; PTB, preterm birth; NICU, neonatal intensive care unit.
Data are median [range], no. of patients (%), or mean±SD unless otherwise specified.
* Congenital anomalies include patent ductus arteriosus.
† Post hoc analysis.

to the nature of the interventions. Attempts to minimize bias included similar patient management in both groups and neonatal assessments by specialists who were unaware of treatment allocation. Third, no patient with a cervical length less than 18 mm was recruited. Therefore, our results might not be applicable for women with twin pregnancies and cervical length less than 18 mm. The reduction of our sample size, after recruitment of the first 98 patients, could affect the power of the study. Lastly, the composite of poor perinatal outcomes was not prespecified and there were many statistical comparisons performed, which can influence risk of alpha error. Therefore, findings from these analyses should be confirmed in other studies.

In conclusion, our randomized head-to-head comparison showed that cervical pessary and 400 mg vaginal progesterone resulted in similar rates of preterm birth before 34 weeks of gestation in women with twin pregnancies and cervical length less than 38 mm. A prespecified subgroup analysis indicated that women with cervical length of 28 mm or less might benefit more from cervical pessary than progesterone.

REFERENCES

1. Martin JA, Hamilton BE, Osterman MJ, Curtin SC, Matthews TJ. Births: final data for 2013. Natl Vital Stat Rep 2015;64:1–65.
2. Iams JD, Goldenberg RL, Meis PJ, Mercer BM, Moawad A, Das A, et al. The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network. N Engl J Med 1996;334:567–72.
3. Heath VC, Southall TR, Souka AP, Elisseou A, Nicolaides KH. Cervical length at 23 weeks of gestation: prediction of spontaneous preterm delivery. Ultrasound Obstet Gynecol 1998;12:312–7.
4. To MS, Fonseca EB, Molina FS, Cacho AM, Nicolaides KH. Maternal characteristics and cervical length in the prediction of spontaneous early preterm delivery in twins. Am J Obstet Gynecol 2006;194:1360–5.
5. Kindinger LM, Poon LC, Cacciatore S, MacIntyre DA, Fox NS, Schuit E, et al. The effect of gestational age and cervical length measurements in the prediction of spontaneous preterm birth in twin pregnancies: an individual patient level meta-analysis. BJOG 2016;123:877–84.

6. Serra V, Perales A, Meseguer J, Parrilla JJ, Lara C, Bellver J, et al. Increased doses of vaginal progesterone for the prevention of preterm birth in twin pregnancies: a randomised controlled double-blind multicentre trial. BJOG 2013;120:50–7.
7. Schuit E, Stock S, Rode L, Rouse DJ, Lim AC, Norman JE, et al. Effectiveness of progestogens to improve perinatal outcome in twin pregnancies: an individual participant data meta-analysis. BJOG 2015;122:27–37.
8. Goya M, de la Calle M, Pratcorona L, Merced C, Rodo C, Munoz B, et al. Cervical pessary to prevent preterm birth in women with twin gestation and sonographic short cervix: a multicenter randomized controlled trial (PECEP-Twins). Am J Obstet Gynecol 2016;214:145–52.
9. Liem S, Schuit E, Hegeman M, Bais J, de Boer K, Bloemenkamp K, et al. Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial. Lancet 2013;382:1341–9.
10. Nicolaides KH, Syngelaki A, Poon LC, de Paco Matallana C, Plasencia W, Molina FS, et al. Cervical pessary placement for prevention of preterm birth in unselected twin pregnancies: a randomized controlled trial. Am J Obstet Gynecol 2016; 214:3.e1–9.
11. Berghella V, Dugoff L, Ludmir J. Prevention of preterm birth with pessary in twins (PoPPT): a randomized controlled trial. Ultrasound Obstet Gynecol 2017;49:567–72.
12. Saccone G, Ciardulli A, Xodo S, Dugoff L, Ludmir J, D'Antonio F, et al. Cervical pessary for preventing preterm birth in twin pregnancies with short cervical length: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2017;30:2918–25.
13. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.
14. Arabin B, Alfirevic Z. Cervical pessaries for prevention of spontaneous preterm birth: past, present and future. Ultrasound Obstet Gynecol 2013;42:390–9.
15. Gates S, Brocklehurst P. How should randomised trials including multiple pregnancies be analysed? BJOG 2004;111:213–9.
16. Saade G, Thom E, Alfirevic Z, Arnaud C, Berghella V, Biggio J, et al. PROMPT: prospective meta-analysis for pessary trials. PROSPERO 2018 CRD42018067740. 2018. Available at: http://ww.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018067740. Retrieved July 5, 2018.
17. McNamara HC, Wood R, Chalmers J, Marlow N, Norrie J, MacLennan G, et al. STOPPIT baby follow-up study: the effect of prophylactic progesterone in twin pregnancy on childhood outcome. PLoS One 2015;10:e0122341.
18. Vedel C, Larsen H, Holmskov A, Andreasen KR, Uldbjerg N, Ramb J, et al. Long-term effects of prenatal progesterone exposure: neurophysiological development and hospital admissions in twins up to 8 years of age. Ultrasound Obstet Gynecol 2016; 48:382–9.
19. Norman JE, Marlow N, Messow CM, Shennan A, Bennett PR, Thornton S, et al. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. Lancet 2016;387:2106–16.
20. van't Hooft J, van der Lee JH, Opmeer BC, van Wassenaer-Leemhuis AG, van Baar AL, Bekedam DJ, et al. Pessary for prevention of preterm birth in twin pregnancy with short cervix: 3-year follow-up study. Ultrasound Obstet Gynecol 2018;51:621–8.

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